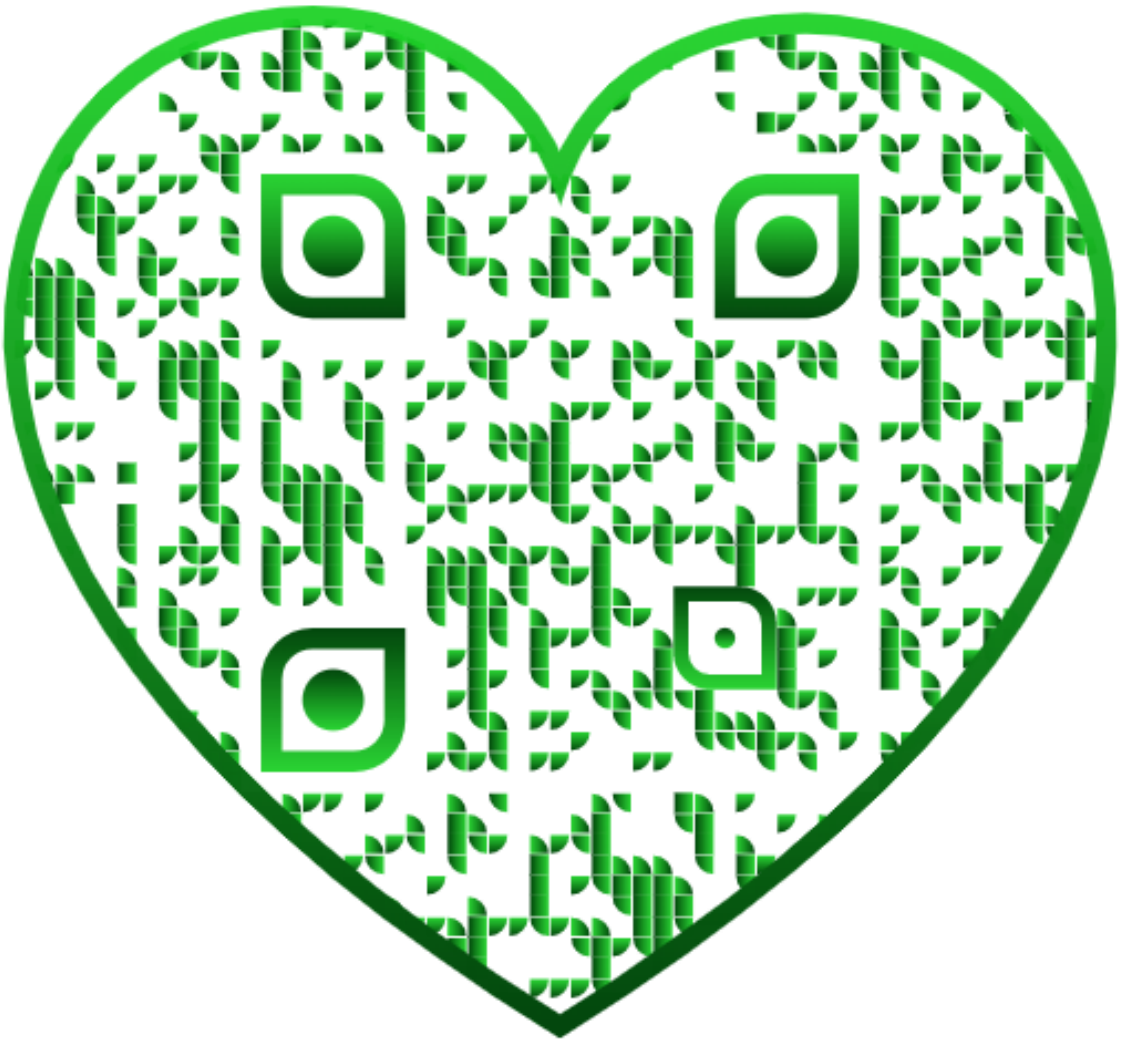
Part-II: Concepts in pharmacokinetics[ADME]

6. Drug absorption
7. Drug distribution
8. Elimination of drug
8.1. Drug metabolism: Phase-I & phase-II reactions, Pharmacogenetic
8.2.Drug excretion: Renal and non-renal excretion
9. Pharmacokinetics Concepts & models
10. Non-linear pharmacokinetics
11. Pharmacokinetics in renal impairment
12. Pharmacokinetics in hepatic dysfunction
13. Pharmacokinetic drug interactions
14. Application of Pharmacokinetics to Clinical Situations
    14.1. Design of dosage regimen
    14.2. Individualization of drug dosage regimens
    14.3. Therapeutic drug monitoring
15. Immuno-suppressants

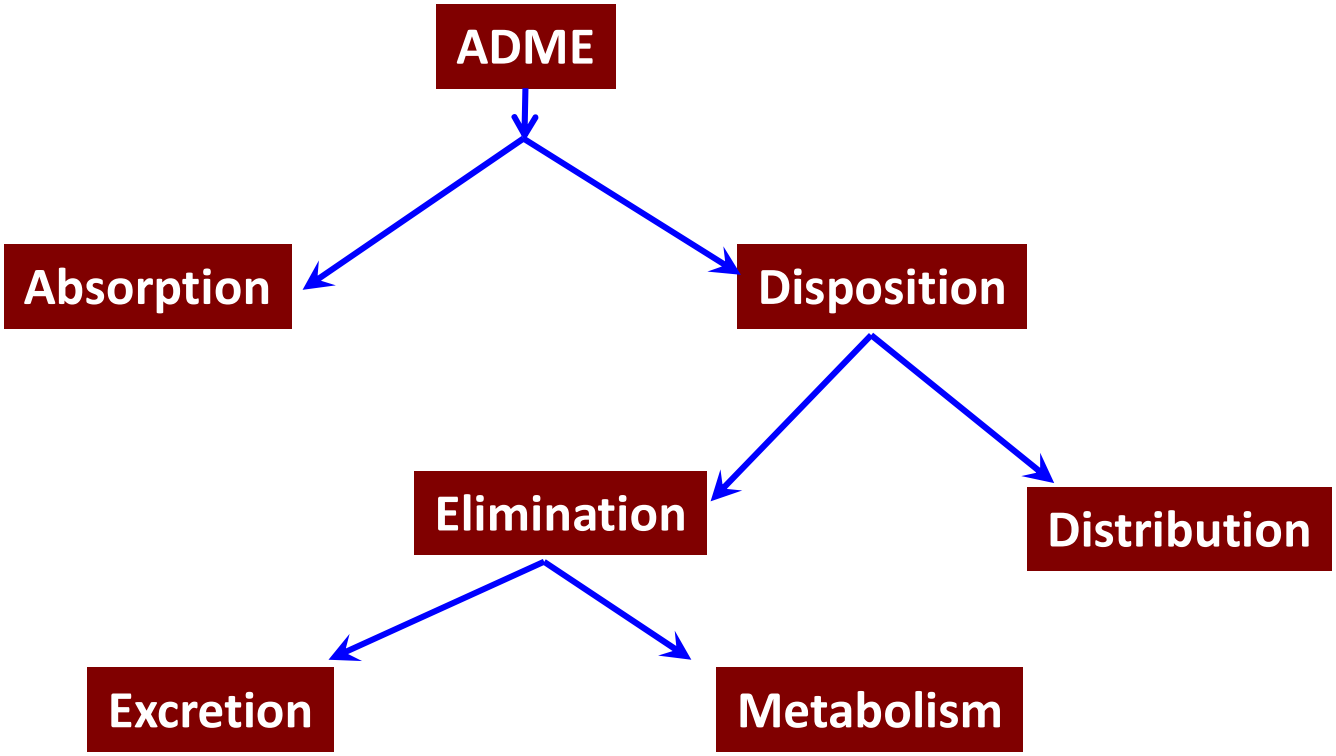


Introduction: What is Pharmacokinetics ?

A. Study of kinetics of drug absorption & disposition

B. Mathematical description of ADME of a drug

C. Quantitative description of how ADME processes affect time course & intensity of response



- Characterization of drug disposition is a vital prerequisite for determination or modification of dosing regimens for individuals and groups of patients based on outcomes of PK study
- The study of pharmacokinetics involves both experimental & theoretical approaches
- Experimental pharmacokinetics involves development of biologic sampling techniques, analytical methods (to measure drugs and metabolites) and data collection and manipulation procedures

- Theoretical aspect of pharmacokinetics involves development of pharmacokinetic models that predict drug disposition after drug administration
- Application of statistics is an integral part of pharmacokinetic studies. Why?

Reasons

Statistical methods are used for:

- data analysis & interpretation
- pharmacokinetic parameter estimation
- designing & predicting optimal dosing regimens for individuals or groups of patients

➢ What is Clinical Pharmacokinetics ?

- It is a discipline that applies PK concepts & principles to design individualized dosage regimens that optimize therapeutic response of a medication while minimizing chance of adverse drug reaction

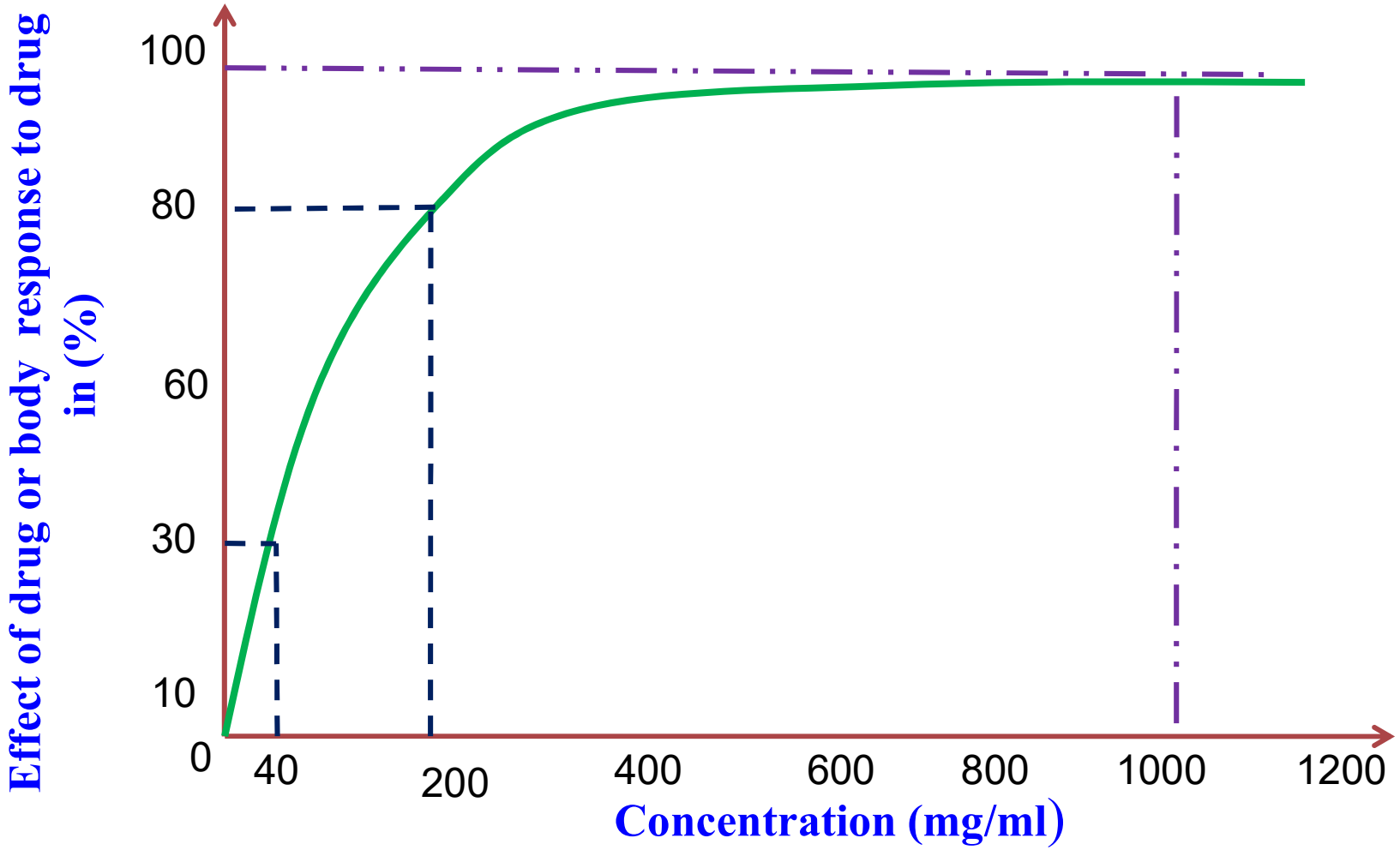
➢ What is pharmacodynamics?

- Relationship b/n drug conc.& pharmacological response

Note:

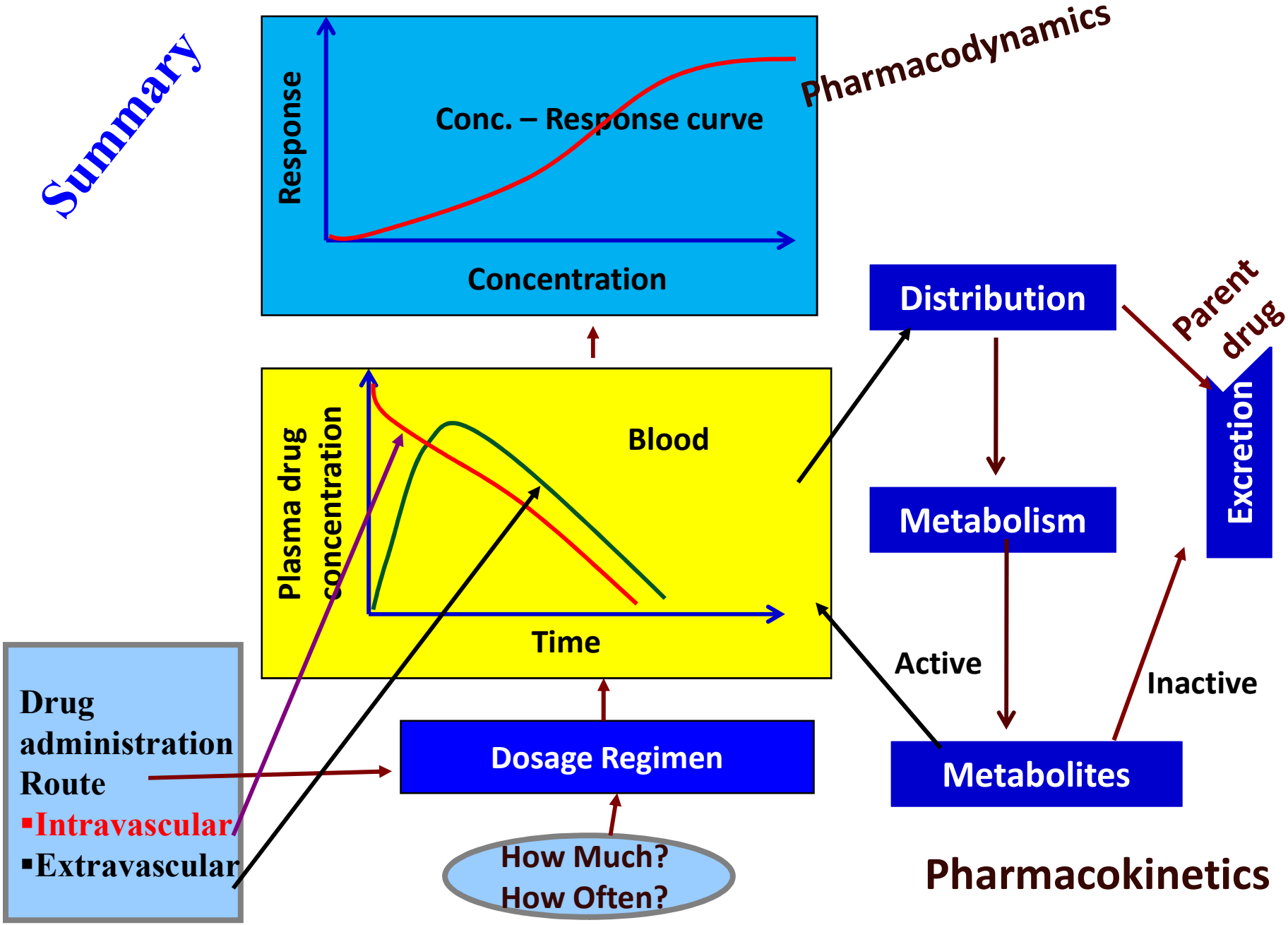
The change in drug effect is usually not proportional to the change in drug dose or concentration

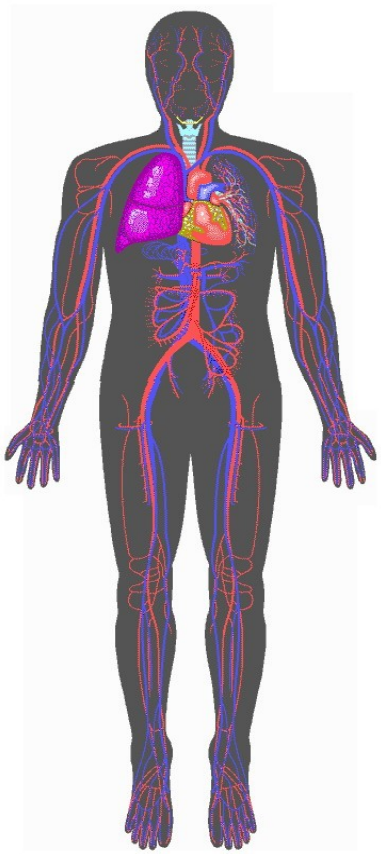
when a drug dose or concentration is increased from a baseline value, the increase in pharmacological effect is greater when the initial dose or concentration is low compared to the change in drug effect observed when the initial dose or concentration is high



The relationship between drug concentration and response is usually a hyperbolic function: The drug effect changes ~50% (from ~30 to 80 units) with a fivefold increase in concentrations at low levels (from ~40 to 200 mg/L), but only ~15% (from ~80 to 95 units) when the same five-fold increase in concentrations is made at high concentrations (from ~200 to 1000 mg/L)

- Therefore, the increase in pharmacological effect that one observes in a patient as the dose is increased is subject to the **law of diminishing returns** and will eventually **reach a maximum**
- The reason that most drugs follow this pattern is because their pharmacological effect is produced by forming a complex with a drug receptor
- Once the drug-receptor complex is formed, the pharmacological effect is expressed
- Often, toxic side effects of drugs follow the same type of dose-response or concentration-response r/ship, albeit shifted to the right on the dose or concentration axis

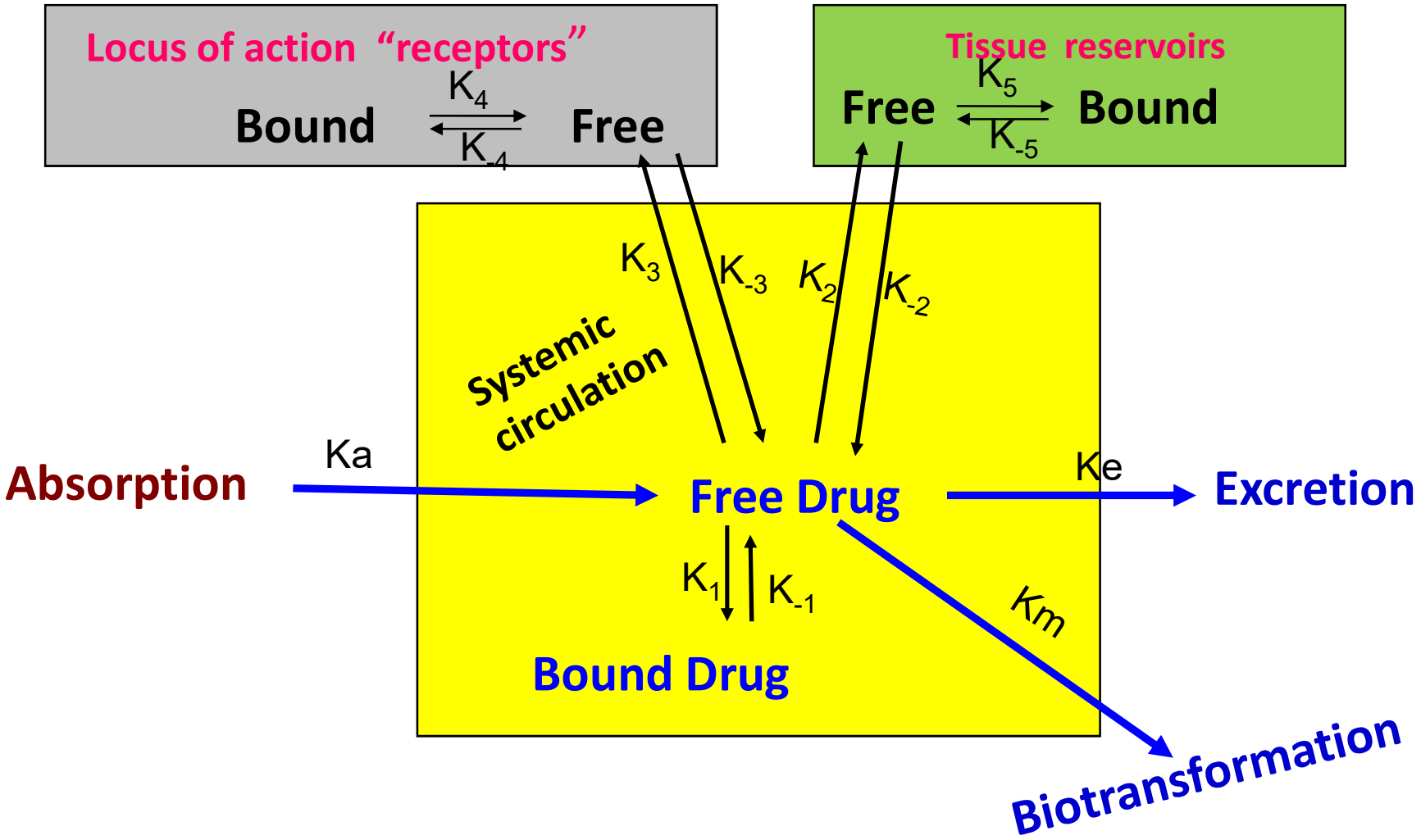

Summary
Response
Conc. – Response curve
Concentration
Pharmacodynamics
Distribution
Parent drug
Excretion
Plasma drug concentration
Blood
Time
Metabolism
Active
Inactive
Drug administration Route
▪Intravascular
▪Extravascular
Dosage Regimen
How Much?
How Often?
Metabolites
Pharmacokinetics



Uses of pharmacokinetics :

- ❖Study the body and organ function
- ❖Study the drug:
  - ➢Fate
  - ➢Distribution / location /penetration
  - ➢Clearance / organs
  - ➢Concentration versus response
- ❖Compare dosage forms [RBA , ABA]
- ❖Quantify interactions
- ❖Defining dosage information
- ❖Population studies
- ❖Study designs

6. Drug distribution :Process by which a drug reversibly leaves blood stream and enters interstitial (extracellular)fluid and/or cells or tissues



Factors affecting drug distribution:

- Blood flow /Blood perfusion
- Capillary permeability
  - ➢Capillary structure [tight versus loose junction]
- Drug solubility[lipid versus water soluble drugs]
- pH-pKa [Ion trapping occurs based on pH gradient of compartments & nature of the drug: basic or acidic]
- Binding of drugs to macromolecules[such as protein, DNA] that hold drug either in blood or other tissues
- Elimination processes [fast versus slow acetylators]
- P-glycoproteins is a cell membrane protein or permeability glycoprotien that pumps drugs out of cells. They affect both absorption & distribution

Blood flow /Blood perfusion

- Distribution of drug to tissues with lower perfusion occurs more slowly
- Accordingly, delivery to muscle, bone, most viscera, skin and adipose is slower and involves a far larger fraction of the body mass
- Distribution of drug to tissues with greater blood flow occurs more quickly, almost instantaneously
- Thus, heart, liver, kidney & brain receive most of the drug during the first few minutes after absorption.

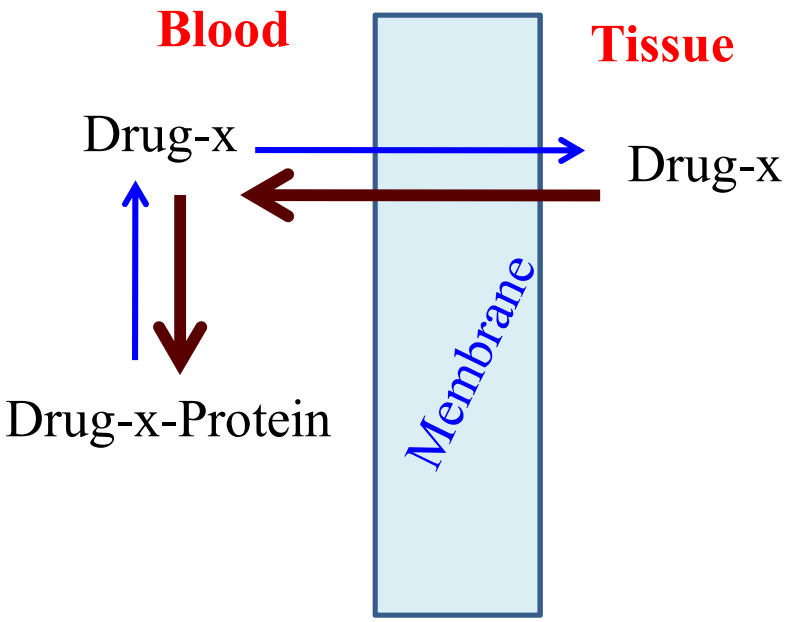
Membrane permeability

- The ability of drug molecules to partition from aqueous to lipid phase of a membrane involves the balance b/n molecules -water & molecules-membrane intermolecular forces
- If attractive forces of molecule-membrane is greater than molecule–water interactive forces, then membrane permeability is relatively higher & vice versa
- Permeability of a cell membrane, for a specific drug, depends on a ratio of its lipid to water solubility
  - Higher lipid to water partition coefficient, implies higher membrane permeability

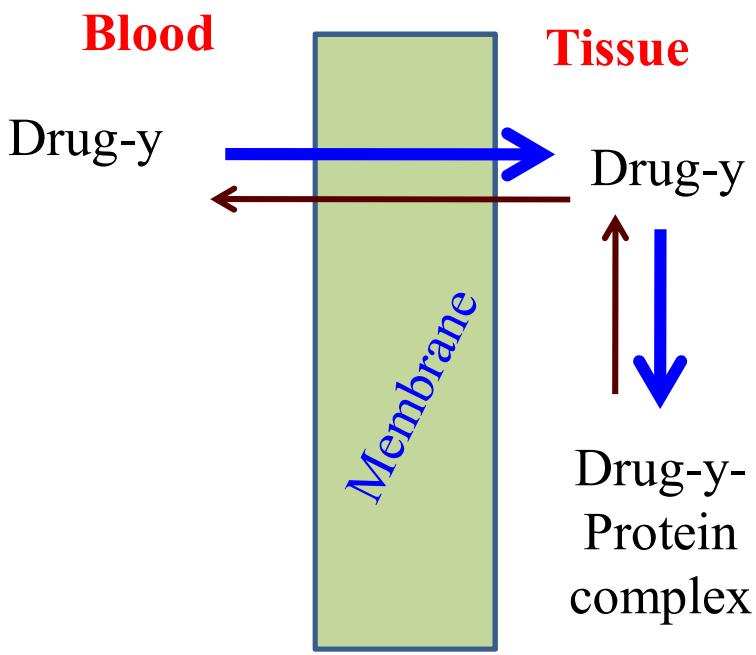
Binding of drugs to macromolecules

- Drugs ordinarily bind to protein in a reversible fashion and in dynamic equilibrium
- Drug bound to protein are called bound drug while unbound ones are called free drug
- Only unbound drugs can diffuse via capillary wall, for systemic effects, be metabolized & excreted
- Bound drugs momentarily inactive & act as a reservoir.
- Many acidic drugs bind principally to albumin, while basic drugs are to α1-acid glycoprotein (α1-AGP)
- Binding of drugs to macromolecules hold drug either in the tissue or blood/plasma
- Has saturation and competitive inhibition

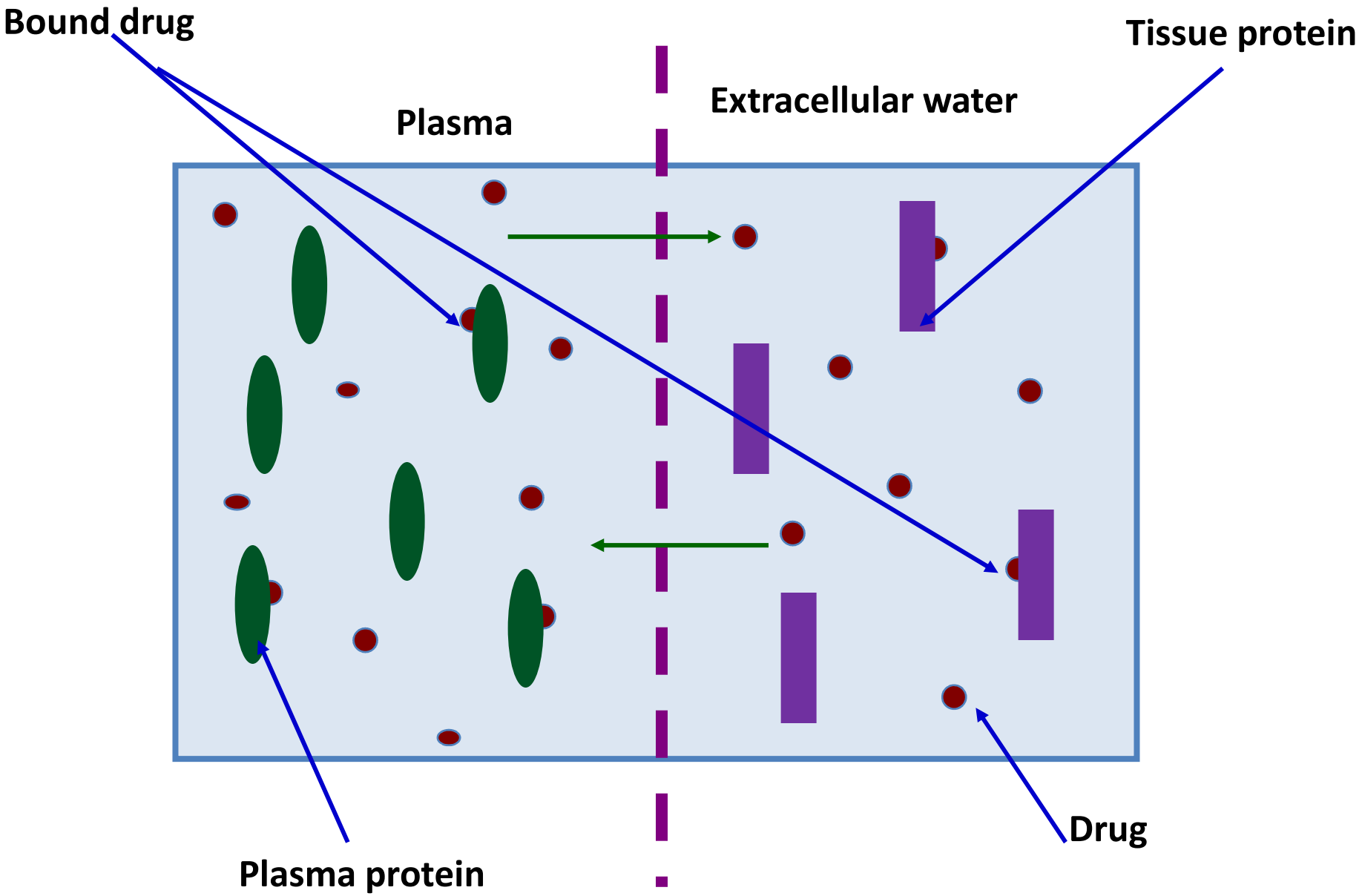
Case-A:high affinity for plasma protein



Case-B-high affinity for tissue protein

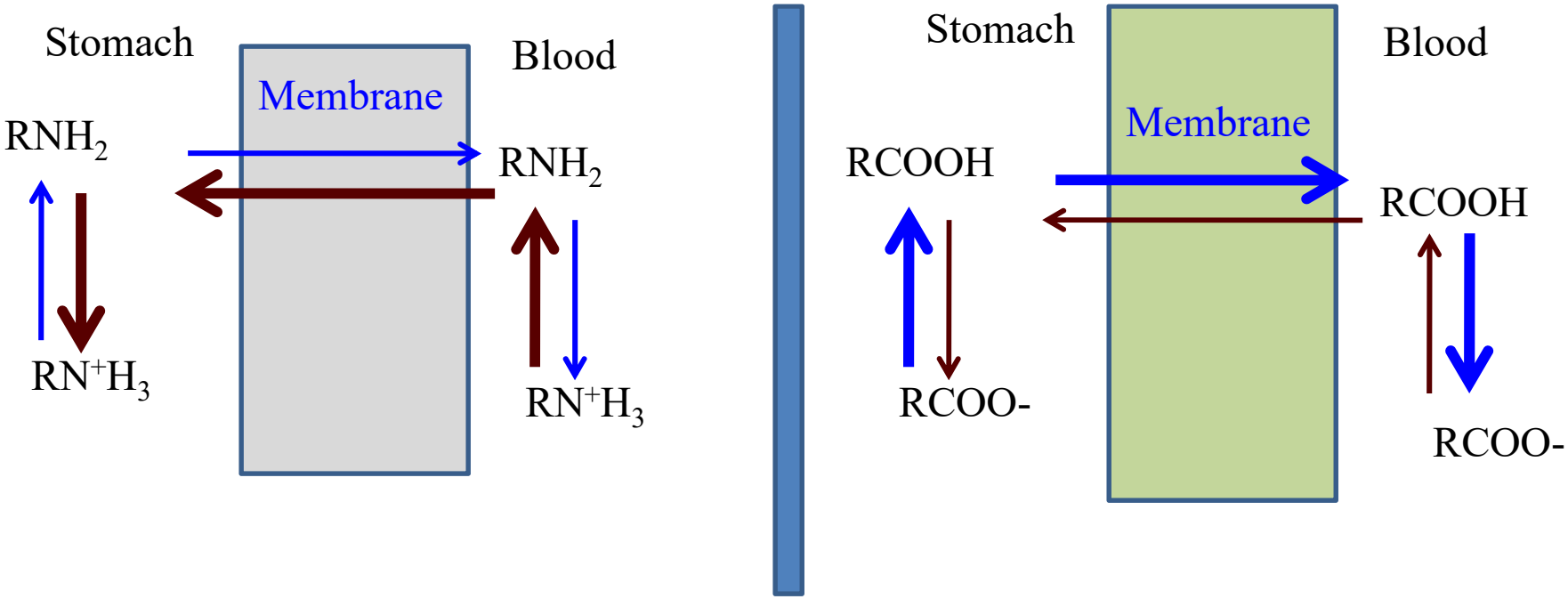


Distribution of drug within the blood or tissue depending on its affinity for binding macromolecules found in the blood or tissues


Bound drug
Tissue protein
Extracellular water
Plasma
Plasma protein
Drug

Ion trapping

Occurs when ionisable drugs encounters pH gradient.



Ion trapping favors accumulation of more of basic drug in the stomach but more of acidic drug in the blood as indicated by bolded arrows

Binding of drugs to blood components

- The major component of blood is RBC
- RBC comprises of 3 components to which drugs bind:
  1. **Haemoglobin** :*Phenothiazines, Pentobarbital, & Diphenylhydantoin*
  2. **Cell membrane** :*Chlorpromazine & Imipramine*
  3. **Carbonic anhydrase:**Chlorthalidone & Acetazolamide

Volume of Distribution [Vd]

- A measure of the tendency of a drug to move out of the blood plasma to some other sites
- The measure of the space available in the body to contain the distributed drug
- Not a true anatomical or physiological volume but apparent volume
- Used merely as a tool to understand **EXTENT** of drug distribution
- Drugs with good affinity for tissue proteins have a high Vd
- Highly plasma protein bound drugs have a low Vd

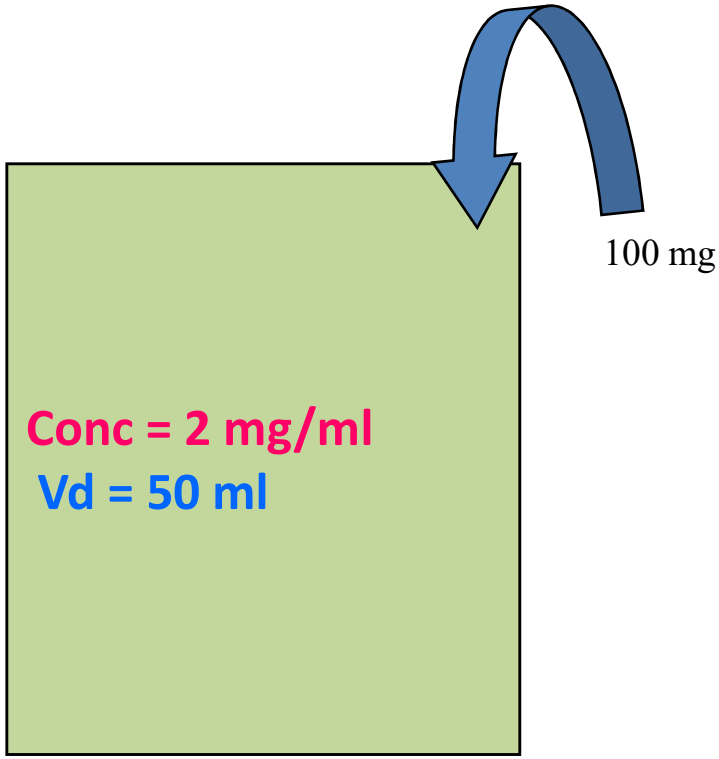
$$V_d = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{D^0b}{C^0p} = \frac{\text{Dose}}{C^0p}$$

Note: Dose is considered if BA of the drug is 100%, otherwise not.

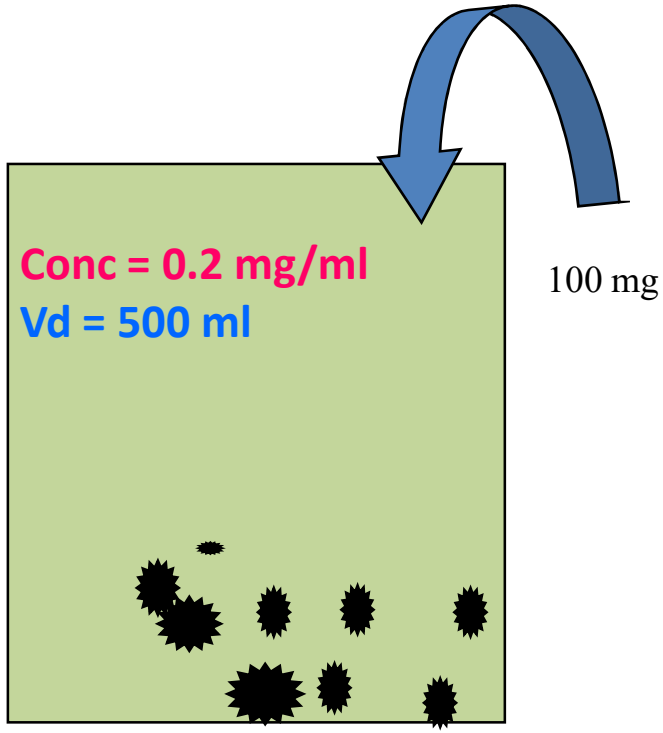
What is the therapeutic significance of volume of distribution?

It enables to determine actual amount of drug dose to be given, so that the intended therapeutic plasma drug concentration can be achieved.

In-vitro pictorial Illustration of Vd



Beaker **without** charcoal



Beaker **with** Charcoal

Examples of drugs along with their Vd

Drug	Vd(L)	Reason	Comment
Warfarin	7	Highly bound to albumin	Mainly retained within blood
Gentamycin	16	Highly polar	
Theophylline	35	13 -25% Albumin bound	Distributed fairly evenly between tissue & blood
Cimetidine	140	Evenly bound to tissue & plasma protein	
Cocaine	140		
Digoxin	510	Strongly bind to tissue proteins	Majority of drug is distributed from blood into tissues
Amitriptyline	1,050	Strongly bind to tissue proteins	
Amiodarone	~5,000	Strongly bound to fat tissue	
Chloroquine	15,000	Strongly bind to DNA	

- V_d is a volume term ,expressed as a simple volume or % of body weight
- If V_d is 5% of body weight, it approximate plasma volume, suggesting drug occupies vascular compartment
- If V_d >100% of body weight, then drug is concentrated in extravascular compartments as in Digoxin: its V_d is 7L/kg, or 700% of body weight
- Magnitude of V_d is a useful indicator for amount of drug outside plasma, the larger the V_d, the greater the amount of drug in the extravascular tissues
- Thus, V_d is a useful parameter in predicting relative amounts of drug in vascular & extravascular tissues
- Given V_d for a particular drug, total amount of drug in the body[D_b] at any time after drug administration may be determined by the measurement of drug concentration in plasma from the equation:

$$D_b = V_d C_p$$

Example

A patient is to be treated with Theophilline. Its salt form , Aminophylline [80% Theophylline & 20% ethylenediamine],with Salt factor, S 0.8. is to be administered to 80 kg patient. Target concentration of Theophylline is 15 mg/L. Mean Vd of Theophylline is 0.48 L/kg. Compute iv dose of Aminophylline

Solution

Given: S = 0.8, Body weight = 80 kg,

target conc. of Theophylline = 15 mg/L

Required: Dose ?

Vd of Theophylline = 0.48 L/kg x 80 kg = **38.4 L**

Parent drug dose = Vd .Co = 38.4 L x 15 mg/L = **576 mg**

Correcting for the salt factor, we have:

Aminophylline dose = Parent drug dose/ Salt factor

= 576 mg/0.8 = **720 mg**

Practice problems

1. Following iv bolus administration of 200 µg of a drug, its initial concentration was known to be 12.5 ng/L. Compute its volume of distribution
2. A 5mg dose of a salt that contains 70% by weight of a parent drug is administered by iv injection. V_d of the drug is 70 mL , find initial plasma drug concentration.
3. The mean volume of distribution of a drug is 0.45L/kg. A salt form that contains 75% by weight of parent drug was administered as iv bolus to a patient that weighs 70 kg. The desirable concentration range for the parent drug is 400-700 ng/ml (i.e. Mid range value is 550ng/ml) What dose of the drug should be administered?

7. Drug biotransformation[or Drug metabolism]

- Phase I & II reactions
- Consequences of enzyme induction & inhibition
- Formation of toxic metabolites
- Factors influencing metabolism
  - ➢Pharmacokinetics
  - ➢Patient conditions[age, sex, nutritional status, disease state, medications & genetic difference]

Biotransformation

- It is a chemical modification of a drug in hepatocytes or extrahepatocytes [adipose, kidneys, lungs & skin tissues] from a lipophilic form (that favors absorption) to a hydrophilic form (that favors excretion) via urine or bile

Results

- ❖ loss of biological activity [Exception is prodrug]
- ❖ Increase in hydrophilicity (H_2O solubility)
- ❖ Promoted drug elimination via renal or other routes

Which one has longer elimination half-life, hydrophilic drug or lipophilic drug? Why?

Drug biotransformation involves two types of reactions

- ❖Phase I reactions
- ❖Phase II reactions

Phase I reaction [asynthetic reaction]

- Mainly takes place in the liver resulting in new or modified functional group formation or cleavage [expose or introduce functional group (–OH, –NH2, – SH or –COOH) to increase reactivity and slightly increase hydrophilicity
- Forms soluble/insoluble inactive metabolites

Drug **Phase I reaction** → inactive metabolite

Exception: Prodrugs **Hydrolysis** → **Active drug**

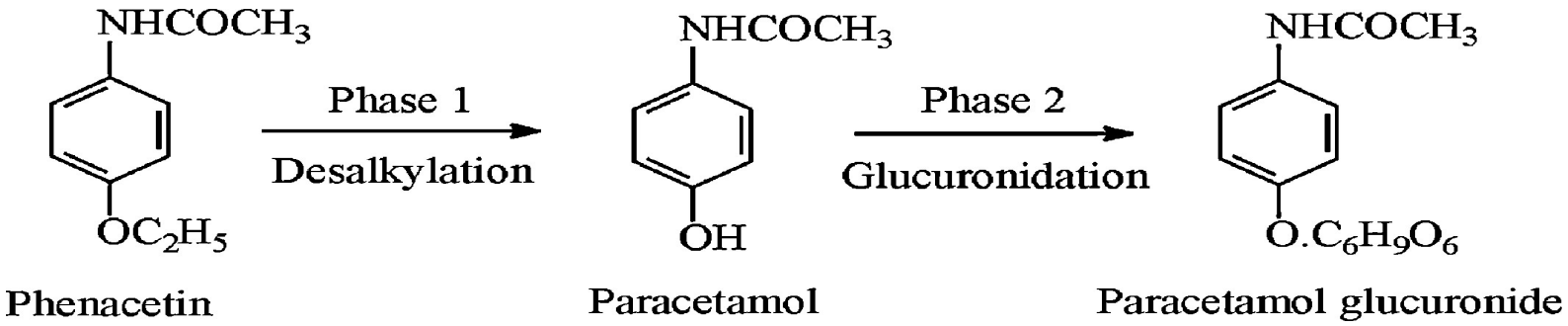
Examples of prodrugs: Codiene, Enalpril, Levodopa

Types of phase I reactions

- Oxidation reaction**
- Hydrolysis reaction
- Reduction reaction
- Dealkylation reaction

Phase II (synthetic) reactions

- Form conjugate products of either the drug itself if it has suitable reactive groups or its Phase I metabolites [insoluble ones] with endogenous substances such as glucuronate, sulfate, acetate, amino acids and reduced glutathione (GSH). Usually, the end products are considerably less pharmacologically active, more water-soluble and more amenable to excretion, than original substance
- Examples of synthetic reactions include Glucuronidation**, Sulfate conjugation, Alkylation [Acetylation or Methylation] & Glycine conjugation reactions.



Phenacetin Paracetamol Paracetamol glucuronide

Pharmacokinetic factors influencing variability in human drug response

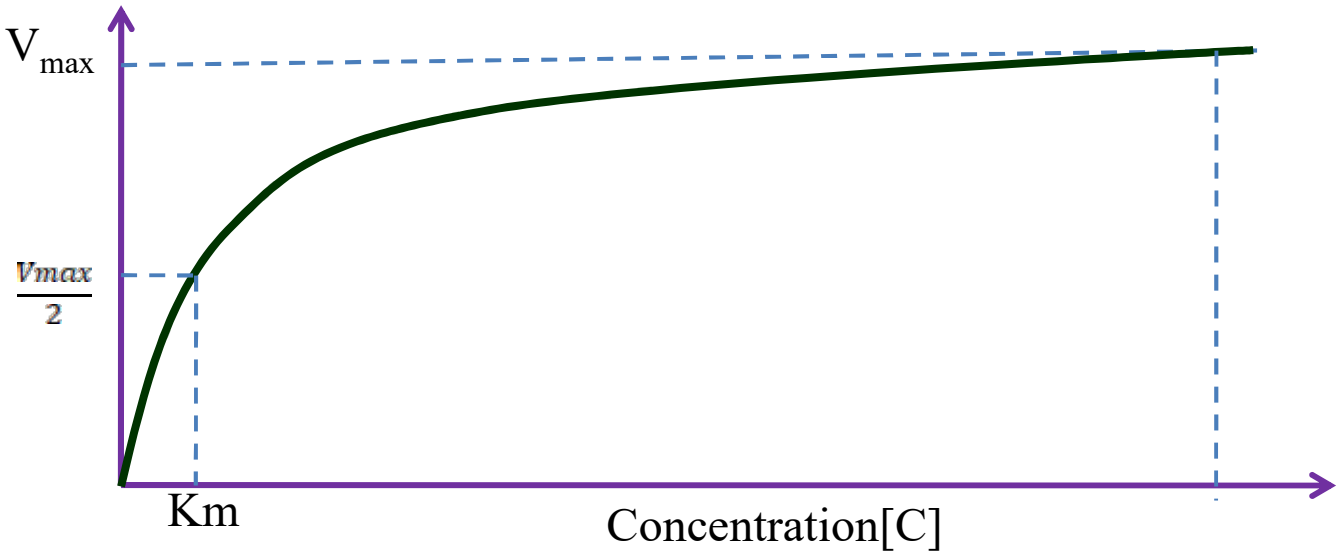
- In general, variability in drug response arises because of inter-individual differences in rates of drug absorption, distribution and elimination
- Degree of drug plasma-protein binding &/or tissue protein binding influences distribution, action, metabolism and renal excretion of drugs
- Thus, changes in plasma protein binding of drugs, e.g. in diseased states, may give rise to altered pharmacokinetic and possibly altered drug response

- **Kinetics of metabolism** involves enzyme drug substrate interaction whereby the substrate combines with enzyme and either dissociates or is converted to products as depicted by *Michaelis–Menten equation*

Enzyme + *Substrate* ⟶ *Complex* ⟶ *Products* + *Enyme*

Michaelis–Menten equation: $v = \frac{[Vmax \cdot C]}{Km + C}$

- As drug concentration is increased enzyme saturation occurs at a reaction velocity, V_{max}, beyond which metabolic reaction occurs at a constant reaction rate.



Note

- **Many phase 1 reactions result in biological inactivation of the drug, forming water soluble or insoluble metabolites**
- **Phase 2 reactions produce a metabolite with improved water solubility and increased molecular weight, facilitating drug elimination from the tissue.**
- **Metabolic kinetics can be first order at lower concentration and zero-order at drug concentration above saturation concentration.**
- **However, since therapeutic plasma drug concentration is very low, most drugs demonstrate first order metabolic kinetics**

Consequences of enzyme induction & Inhibition

Enzyme induction

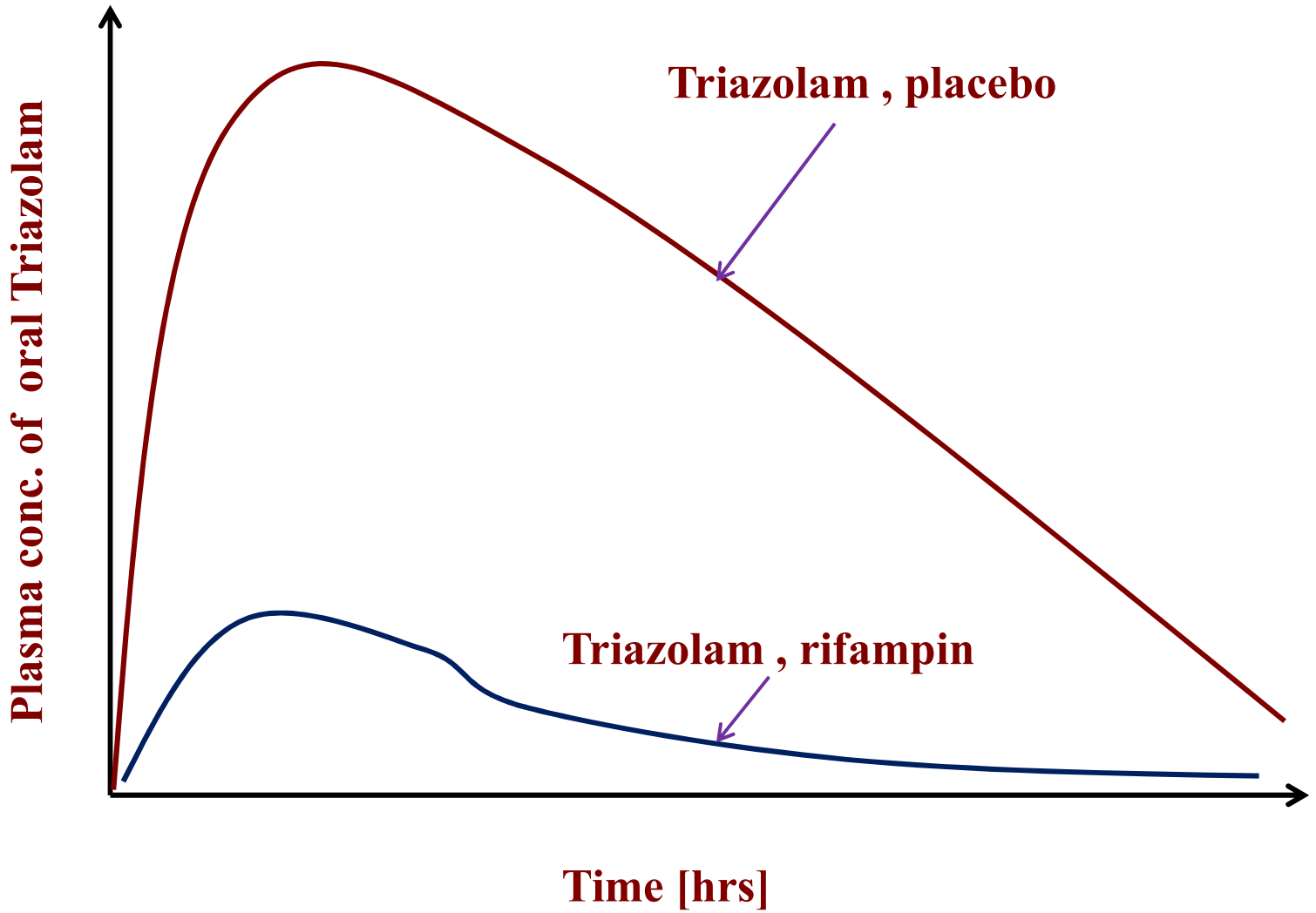
- Accelerate biotransformation of drugs
- Cause therapeutic failure

If drug A is metabolized by microsomal enzymes, then concurrent administration with a microsomal inducer (drug B) will result in enhanced metabolism of drug A.

Examples of enzyme inducers:

Rifampicin, Phenytoin, Sulfonamide, Barbiturate, etc

e.g. Warfarin + Barbiturate → ↓ anticoagulation



Plasma conc. of Triazolam in 10 persons after 0.5 mg oral Triazolam after pretreatment with 600 mg with rifampin per day and placebo for 5 days

Enzyme Inhibition

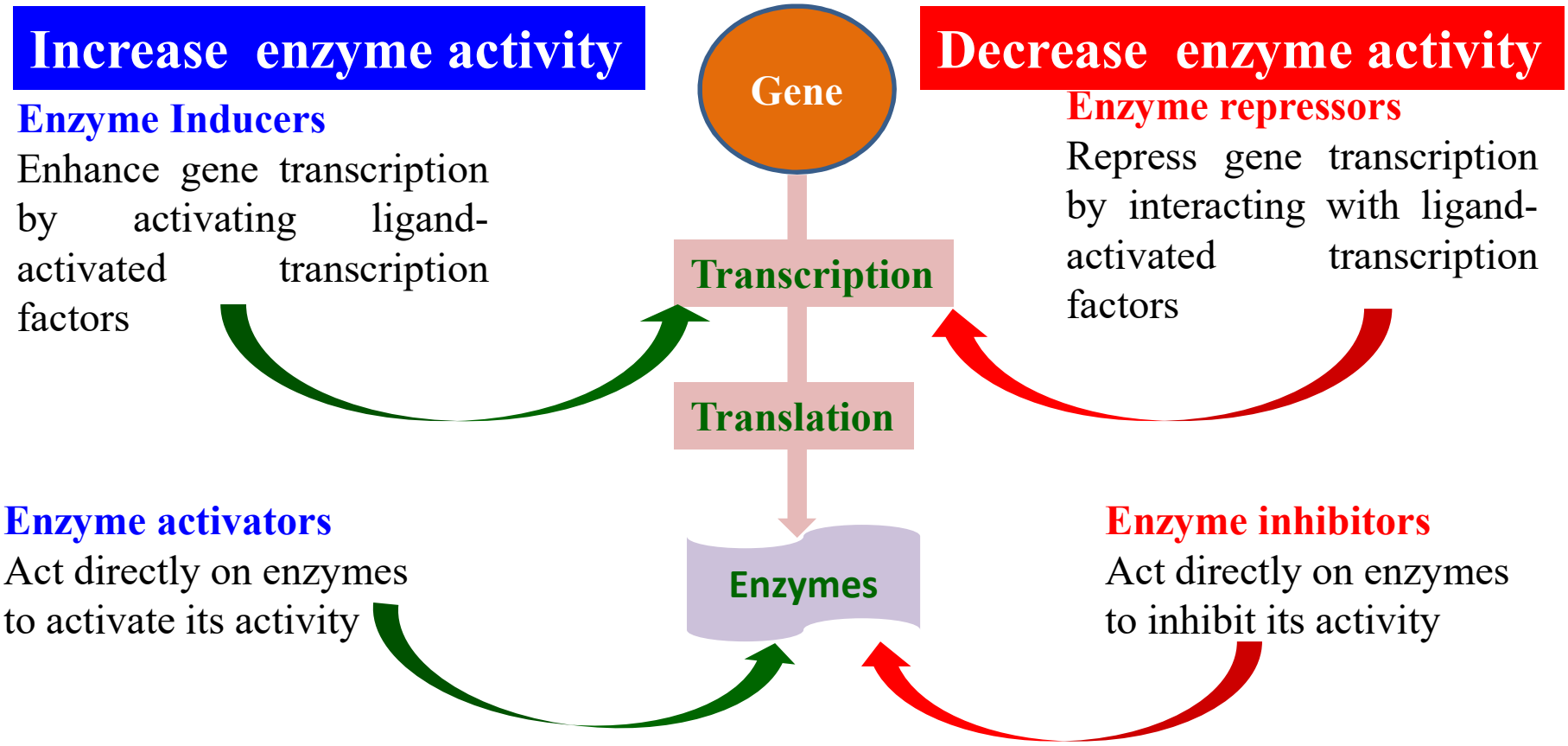
- Delays biotransformation of drugs
- Reduced clearance of drugs
- prolonged half-life of drugs
- Drug accumulation
- Increases intensity, duration of action and some times toxicity or severe adverse effects

Examples of enzyme inhibitors:

Metronidazole, Isoniazid, allopurinol, cimetidine, etc

Example: Warfarin + cimetidine → Haemorrhage

Major mechanisms that increase or decrease enzyme activity



Patient related factors

A. Age

- Differences in drug metabolic rate in different age groups is mainly due to variations in enzyme content, enzyme activity & hemodynamics
- In neonates & infants microsomal enzymes are not fully developed, drugs are slowly biotransformed

  Example: CAF leads to cyanosis or gray baby syndrome in infants
- In very elderly persons, liver size, microsomal enzyme activity and cardiac output hence hepatic blood flow are reduced, leading to reduced drug metabolic rate

B. Diet

A number of dietary components alter enzyme content & activity

- ❖Low protein & high protein diet decreases & increases drug metabolizing rate, respectively.
- ❖High protein to carbohydrate [CHON to CHO] ratio enhances drug metabolism
- ❖Fat free diet depresses CYP-450 levels since phospholipids which are vital components of microsomes are deficient
- ❖Dietary deficiency of vitamins[A,B_2,B_3, C, E] & minerals [Fe, Ca, Mg, Cu & Zn] retard enzymes metabolic activities

C. Disease states

- All pathologic conditions associated with liver such as hepatic carcinoma, hepatitis, cirrhosis, obstructive jaundice, etc **enhance half-lives of almost all drugs**
- Renal diseases impair such biotransformations as glycine conjugation of salicylates, oxidation of vitamin D & hydrolysis of procaine.
- CHF & MI impair metabolism of drugs having high hepatic extraction ratio such as propranolol, lidocaine
- In diabetes, glucuronidation is reduced due to decreased availability of Uridine diphosphoglucuronic acid [UDPGA]

D. Pharmacogenetic factors

Pharmacogenetics is the study of intersubject variability in terms of rate of drug distribution & disposition hence drug response [therapeutic or adverse] to normal dose due to genetic differences.

Examples:

- **Slow acetylators** are more likely to experience toxic reactions with normal doses of drugs while **fast acetylators** may remain under therapeutic with same drug dose
- **Oxidative drug metabolism** varies substantially (20-fold) between patients, so some patients fail to respond to doses of drugs that cause unacceptable side-effects in others

8. Excretions of drugs

- Excretion involves irreversible removal of drugs &/or their metabolites from the body
- The principal organs of excretion are kidneys
- Nonrenal excretions occur via lungs, bilary system, intestine, salivary glands, sweat glands
- The rate of excretion influences duration of drug action
  - Drug with slow rate of excretion will have effects that persevere for longer period

- Renal filtration
- Renal Active secretion

} Mechanisms of excretion

- Bilary excretion
- Entero-haepatic circulation

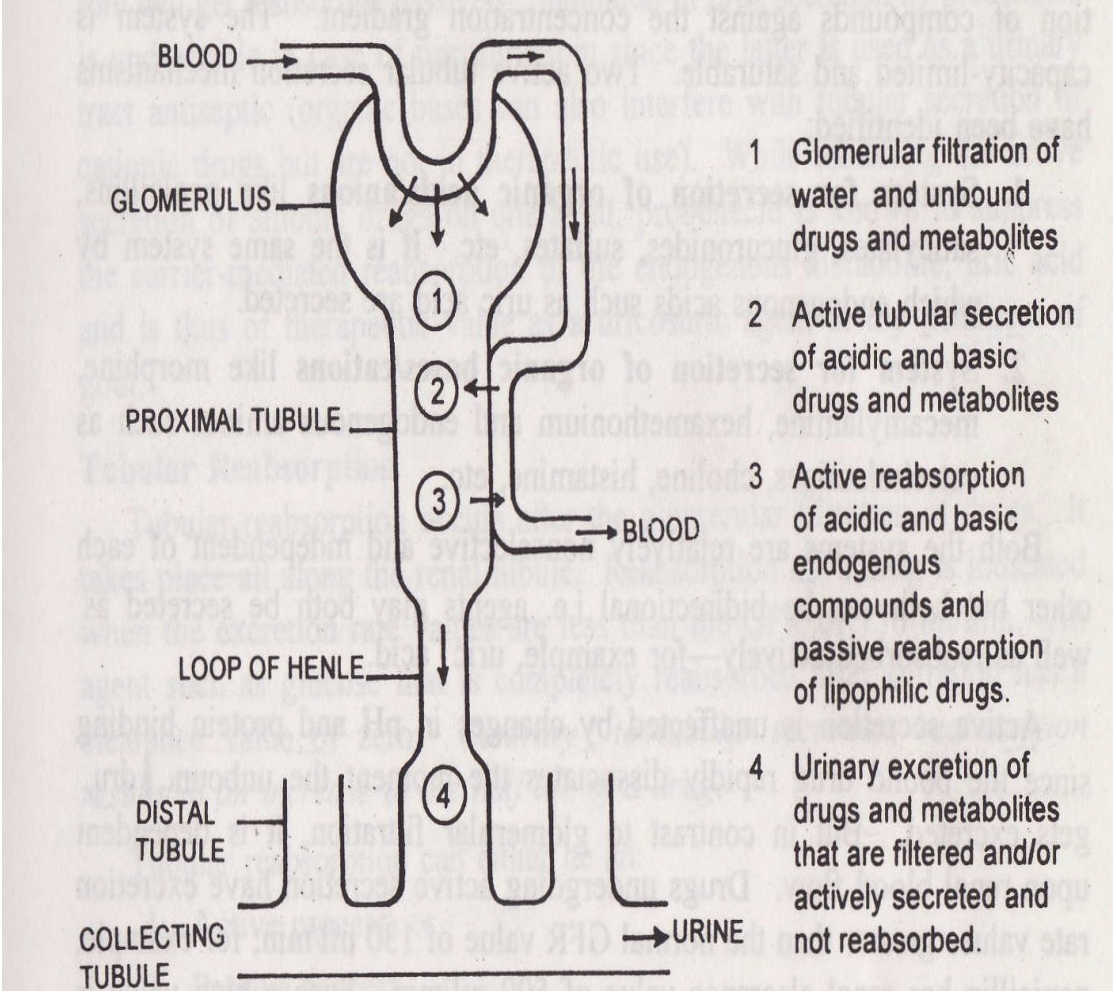
} Partial excretion

Renal excretion occurs by:

- Glomerular filtration[GF]
- Active tubular secretion [ATS]

Note

- GF& ATS remove drug out of the body, while tubular reabsorption retains drug in the body


BLOOD
GLOMERULUS
1
2
PROXIMAL TUBULE
3
BLOOD
LOOP OF HENLE
4
DISTAL TUBULE
COLLECTING TUBULE
URINE
1 Glomerular filtration of water and unbound drugs and metabolites
2 Active tubular secretion of acidic and basic drugs and metabolites
3 Active reabsorption of acidic and basic endogenous compounds and passive reabsorption of lipophilic drugs.
4 Urinary excretion of drugs and metabolites that are filtered and/or actively secreted and not reabsorbed.

Rate of Excretion = Rate of filtration + Rate of secretion - Rate of reabsorption

Glomerular filtration depends on:

- concentration of drug in the plasma
- molecular size, shape and charge of drug
- glomerular filtration rate

- All plasma protein unbound drugs can pass through glomerulus
- All drugs with low molecular weight can pass through glomerulus

e.g. Digoxin, Ethambutol

Active tubular secretion

- The cells of the proximal convoluted tubule actively transport drugs from the plasma into the lumen of the tubule

Example of drugs that actively secreted into cells of proximal convoluted tubule

- Acetazolamide
- Benzyl penicillin
- Dopamine
- Pethidine
- Thiazides
- Histamine
- etc.

Tubular reabsorption

- The reabsorption of drug from lumen of distal convoluted tubules into plasma occurs either by simple diffusion or by active transport.
- Lipophilic drugs are extensively under go passive reabsorption while polar drugs are not.
- Diffusion of weak electrolytes via lipoidal tubular membrane depends upon degree of ionization which in turn depends on pH of the urine & pKa of the drug
- When urine is acidic, the degree of ionization of basic drug increase & their reabsorption decreases
- When urine is more alkaline, the degree of ionization of acidic drug increases & their reabsorption decreases.
- Passive absorption of weakly acidic drugs occur from acidic urine while that of basic drugs occur from a urine with basic pH.

Note: Urine pH fluctuate from pH 4.5 to 7.5 depending upon diet, drug intake & renal pathophysiology of the patient.

Summary of combined effect of urine pH & drug pKa and lipid solubility on reabsorption of drug

1. An acidic drug such as penicillin or a basic drug such as gentamicin which is polar in its unionized form, is not reabsorbed passively, irrespective of the extent of ionization in urine. Excretion of such drugs is indpendent of pH of urine & its flow rate. Their rate of excretion is the sum of rate of filtration & rate of active secretion
2. Very weakly acidic, nonpolar drugs (pKa>8) such as Phenytoin or very weakly basic , nonpolar drugs (pKa<6) such as propoxyphene are mostly unionized throughout the entire range of urine pH. Thus, they reabsorbed passively at all values of pH.

   The rate of excretion of such drugs is always low & insensitive to urine pH

3. A strong acidic drug (pKa ≤2) such as cromoglycic acid or a strongly basic drug (pKa≥12) such as guanethidine is completely ionized at all values of urine pH. Thus, not reabsorbed. Their rate of excretion is always high & intensive to pH of urine
4. Only for an acidic drug in the pKa range 3 to 8 such as NSAIDs and for a basic drug in the pKa range 6 to 12 such as Morphie analogs, tricyclic antidepresants the extent of reabsorption is greatly dependent upon urine pH & varies negligible to almost complete

Example

The amount of dexamphetamine excreted in urine varies from 3 to 55% of administered dose as urine pH varies from 8 to 5.

Drug	Acidic filtrate	Renal tubule wall	Alkaline filtrate
Weak Acid, HA pKa 3 to 8	Negligible Ionization $H^+ + A^-$ ⟷ HA	**Drug reabsorbed passively** **HA** ↕ **$H^+ + A^-$**	Significant Ionization HA ⟷ $H^+ + A^-$ ↓ Drug lost in urine
Weak base, BOH pKa 6- 12	Significant Ionization $B^+ + OH^-$ ⟷ BOH ↓ Drug lost in urine	**Drug reabsorbed passively** BOH ← BOH ↕ $B^+ + OH^-$	Negligible Ionization BOH ⟷ $B^+ + OH^-$

Impact of urinary pH on excretion of weakly acidic & weakly basic drugs
Note: Bolded arrows show predominant processes

Enterohepatobiliary excretion

- The cycle in which the drug is absorbed, excreted into the bile, and reabsorbed is known as enterohepatic circulation
- Conjugated & polar drugs are excreted by hepatocytes into bile
- Excretion of drugs through bile provides a back up pathway when renal function is impaired
- From drug excreted through bile into intestine, some amount of drug is reabsorbed into portal vessel leading to an enterohepatic cycling & prolong drug action

e.g. Tetracyline, CAF, oral estrogen, Doxycycline, Diazepam, Digoxin are secreted into bile & largely reabsorbed hence have long duration of action

Note

- Drugs with molecular weights in excess of 500 are excreted mainly in the bile
- Drugs with molecular weights 300 to 500 are excreted both in urine and in bile. For these drugs, a decrease in one excretory route results in a compensatory increase in excretion via the other route
- Parent drugs &/or metabolites that excrete into bile must have high molecular weight and strongly polar
- Compounds that stimulate bile production & /or glucuronidation enhance biliary excretion of drugs or conjugated metabolite which normally eliminated by this route
- Orally administered drugs are more extracted by the liver into the bile than the same drugs given intravenously
- Compounds with molecular weights of less than 300 are excreted almost exclusively via the kidneys into urine

Gastrointestinal excretion

- When a drug is administered orally, a part of the drug is not absorbed but excreted in the faeces.
- The drugs which do not undergo enterohepatic cycle after excretion into the bile are subsequently passed with stool.

For instance:

- $Al(OH)_3$ changes stool into white colour
- Ferrous sulfate changes stool into black
- Rifampicin changes stool to orange red.

Pulmonary excretion

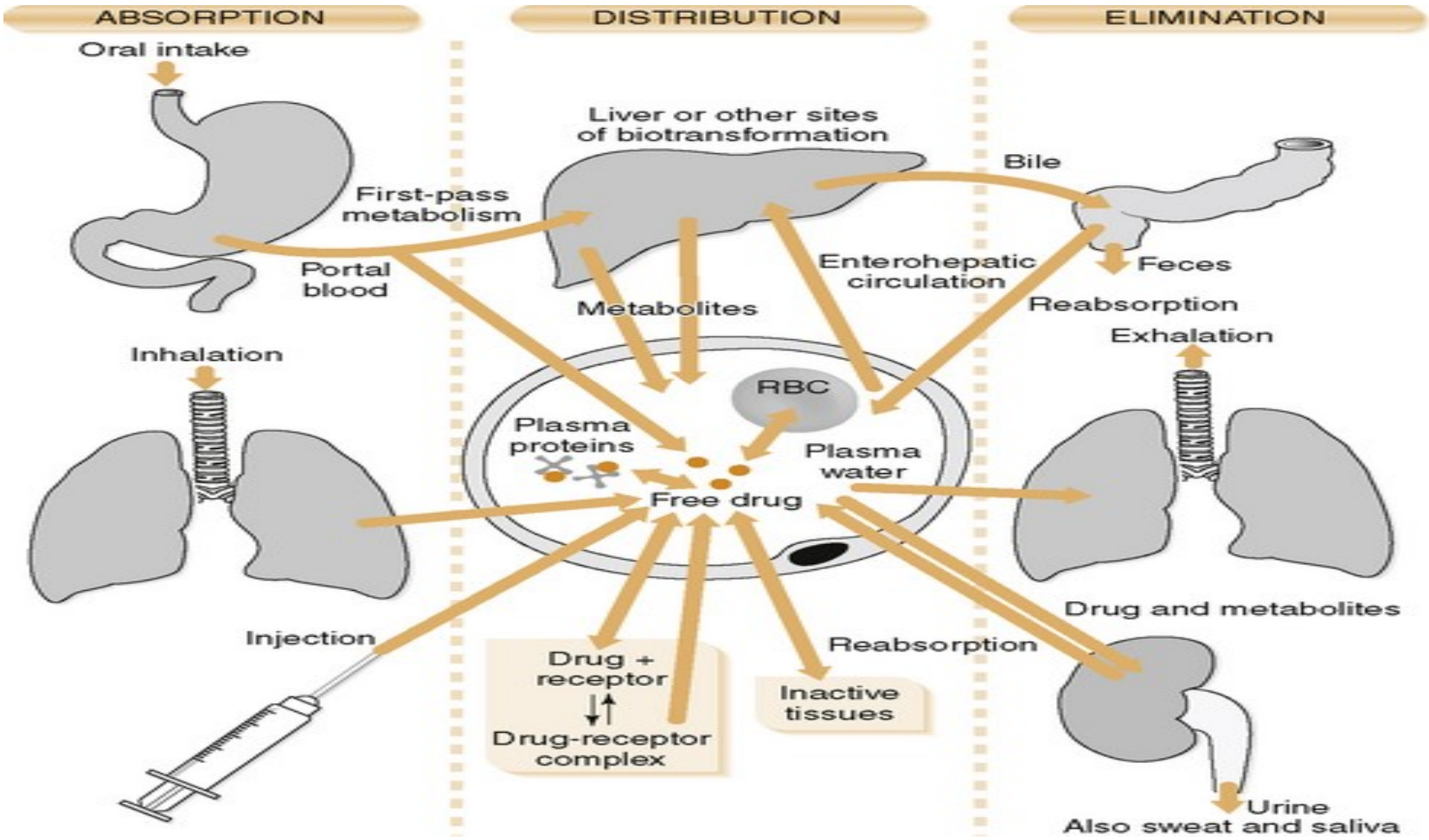
- Readily vaporizable drugs, such as inhalation, alcohols and anaesthetics are excreted through lungs
- Rate of drug excretion through lung depends on:
    - ❖volume of air exchange
    - ❖depth of respiration
    - ❖rate of pulmonary blood flow
    - ❖drug concentration gradient

Mammary excretion

- Many drugs mostly **weakly basic drugs** are accumulated into the milk.
- Therefore lactating mothers should be cautious about the intake of these drugs because they may enter into baby through breast milk and produce harmful effects in the baby

e.g. ampicillin, aspirin, chlordiazepoxide, coffee, diazepam, furosemide, morphine, streptomycin

Summary of pharmacokinetic concepts



9. Pharmacokinetics: Basic concepts and models

9.1. Pharmacokinetics: Basic concepts

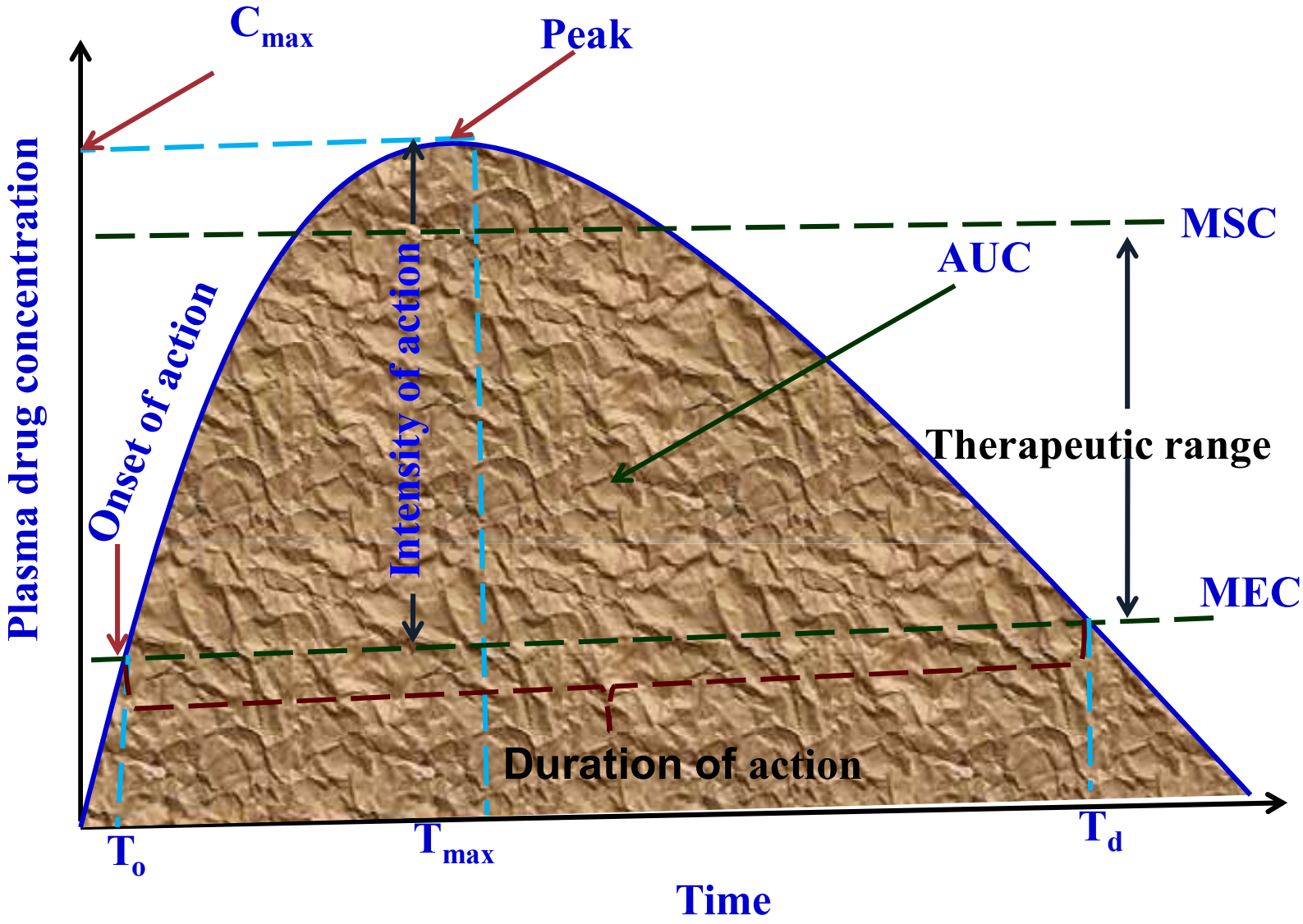
Definitions

Dosage regimen

- Frequency of administration of a drug in a particular dose
- Both dosage regimen & duration of therapy depends on therapeutic objective

Plasma drug concentration –time profile

- Obtained after administration of a single dose of a drug
- It depicts a direct relationship between drug concentration in the plasma & at site of action
- It shows various PK & PD parameters



Plasma drug concentration –time profile

Pharmacokinetic parameters

1. **C_{max}** is a peak plasma drug concentration, peak height drug concentration or maximum drug concentration that occurs at point of maximum plasma drug concentration called the peak. Peak level depends upon dose size & rates of drug absorption & elimination. At peak point ,drug absorption rate & elimination rate are equal. Peak concentration is related to intensity of pharmacologic response
2. **T_{max} :**The time for drug to reach peak plasma drug concentration after extravascular drug administration. Useful to estimate rate of drug absorption. Helpful in assessing efficacy of drug used to treat acute conditions
3. **AUC**: Represents total integrated area under plasma level time profile. It expresses total amount of drug that comes into systemic circulation after its administration. Most important PK parameter in evaluating BA of drug from its dosage form since it represents extent of drug absorption. It is useful to evaluate intensity of drugs used for treatment of chronic conditions.

Pharmacodynamic parameters

1. **Minimum effective concentration[MEC]:** Minimum plasma drug concentration required to produce therapeutic effect. It reflects the minimum drug concentration at the receptor site to elicit the desired pharmacologic response. Drug concentration below MEC is said to be in the subtherapeutic level. In the case of antibiotics, it is called Minimum Inhibitory Concentration[MIC] as it describes the minimum plasma antibiotic concentration required to inhibit microbial growth or kill microorganisms.
2. **Maximum safe concentration[MSC] or Minimum Toxic concentration[MTC].** It is plasma drug concentration above which adverse or unwanted effects precipitated. Drug concentration above MSC is in the toxic level.
3. **Onset Time**: The time required for the drug to start producing pharmacologic response. It is the time for the drug plasma concentration to reach MEC after drug administration

4. **Onset of action:** Refers to the beginning of pharmacologic response. It occurs when plasma drug concentration just exceeds required MEC
5. **Duration of action:** The time period for which plasma drug concentration remains above the MEC level
6. **Intensity of action/ Peak response:** It is the maximum pharmacologic response produced by the peak plasma concentration of drug
7. **Therapeutic range:** Represents drug concentration between MEC & MSC

Rate, Rate constants and orders of reactions

Pharmacokinetics is the mathematical analysis of ADME processes. The movements of drug molecules from the site of application to the systemic circulation via various biologic barriers, their conversion into metabolite & finally their exit out of the body can be expressed mathematically by the rate at which they proceed, the order of such processes & rate constants.

Rate: The velocity with which a reaction or process occurs. Consider the chemical reaction: drug A ⟶ drug B

- Rate of forward reaction is expressed as –dA/dt while the rate at which drug B is formed is expressed as dB/dt.
- Experimentally rate of reaction is determined by measuring the decrease in concentration of drug A with time t.

Order of reaction/ order of process: refers to the manner in which concentration of drug [reactants] influence the rate of reaction or process

- If C is concentration of drug A, the rate of decrease in C of drug A as it is changed to B can be given as a function of time t.

$$\frac{dC}{dt} = -KC^n$$

Where n is 0,1,2,... indicating order of reaction,
K is rate constant and dc/dt is rate of reaction

- The three commonly encountered rate processes in a physiologic system are zero-order process, first-order process and mixed-order process

- The pharmacokinetics of most drugs can be adequately described by first order processes

Zero-order kinetics or Constant rate process

Defined as the one whose rate is independent on concentration of drug under going reaction, i.e, the rate of reaction cannot be increased further by increasing concentration of reactants.

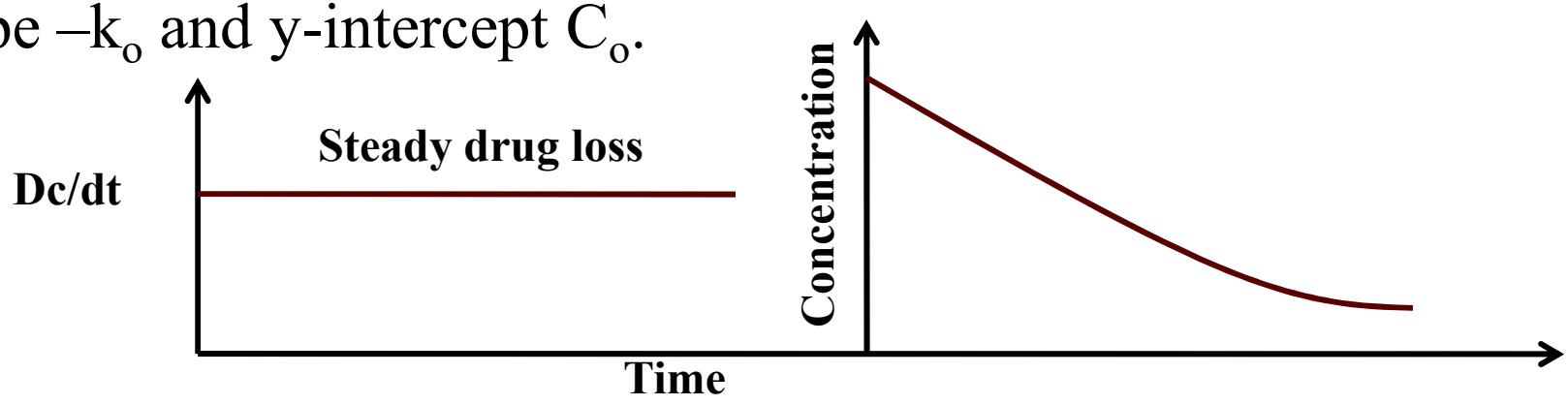
$$\frac{dC}{dt} = -KC^{o} = -K_o$$

After rearranging & integrating, we have a linear equation:

$$C_t = C_0 - K_0 t$$

Interpretation of the linear equation: Concentration, C of reactant [drug] decreases linearly with time, t.

A plot of concentration C versus time t is a straight line with slope $-k_o$ and y-intercept C_o.



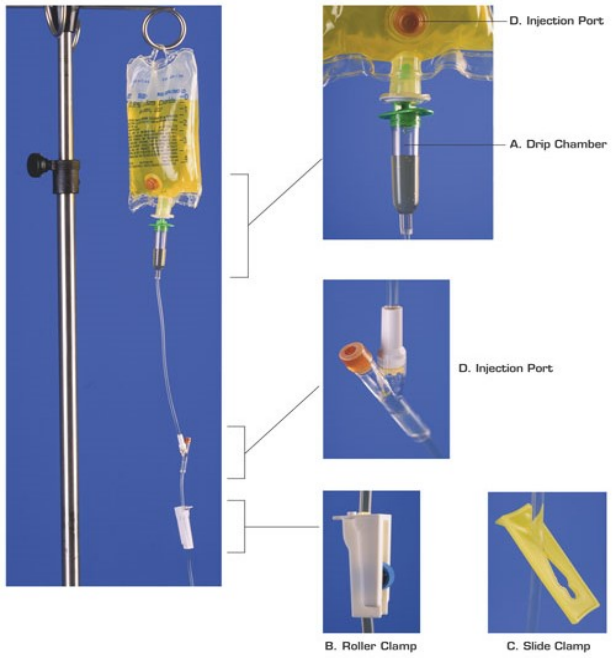
- **Half time or Half-life [$t_{1/2}$]:** Time required for initial concentration of a drug to decline by 50%.

$$t_{1/2} = \frac{C_o}{2K_o}$$

- Half-life of a zero-order process is not constant, thus, it has little practical importance

Example of zero-order process

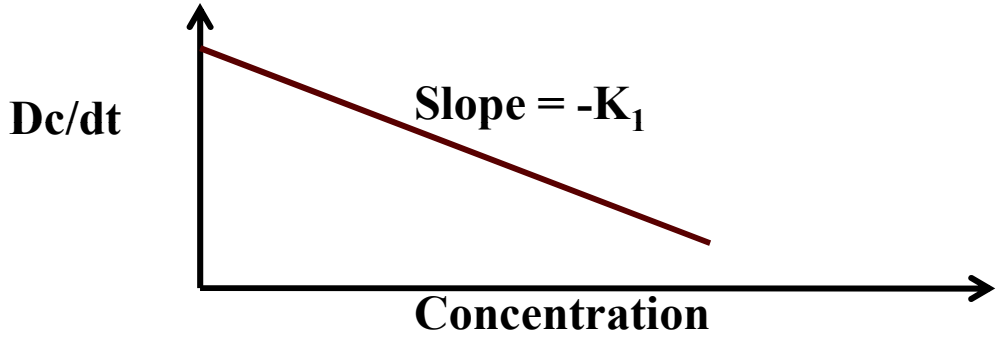
- Rate of Metabolism/drug-protein binding/ enzyme or carrier mediated transport remain constant as long as its concentration is in excess of saturation concentration
- Administration of a drug product as a constant intravenous infusion
- Controlled drug delivery from intramuscular implants , osmotic pump, etc



First order kinetics

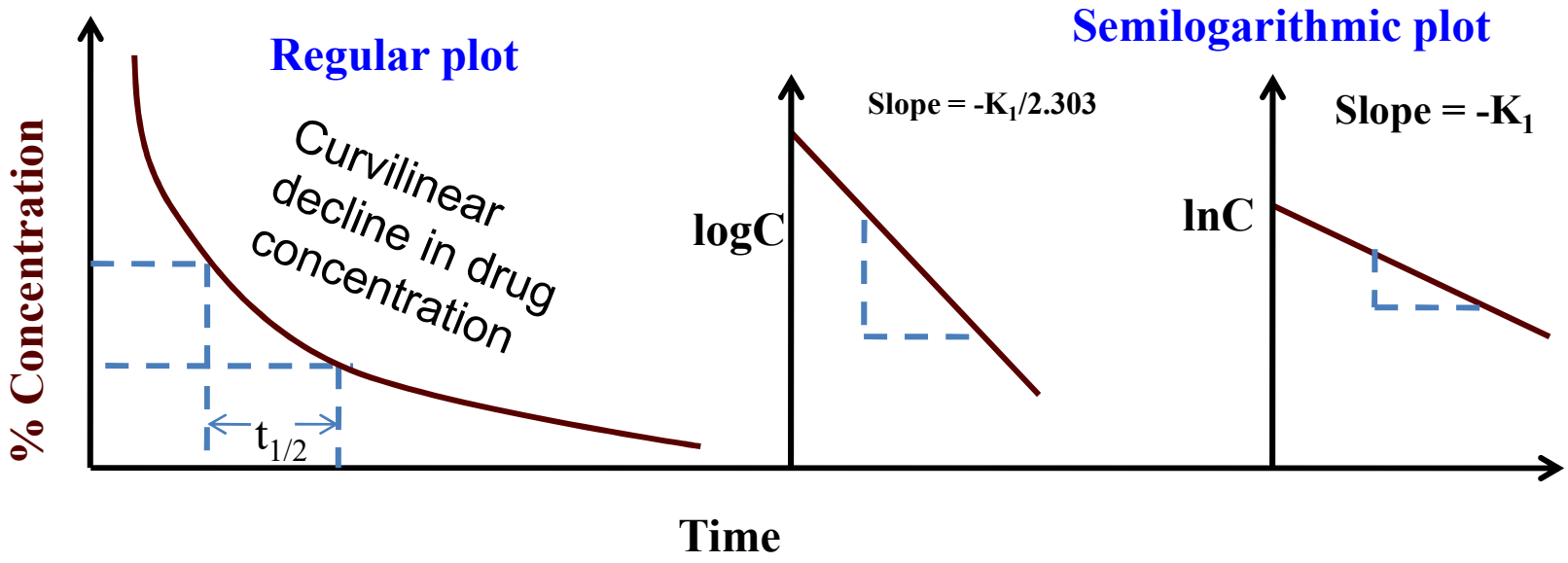
$$\frac{dc}{dt} = -K_1 C$$

The rate of first order process is directly proportional to the concentration of drug under going reaction, i.e, the greater the concentration the faster the reaction. Thus first order process follows linear kinetics



First order kinetics showing linear relationship b/n rate of reaction & drug concentration

The first order process which is monoexponential rate process is characterized by logarithmic or exponential kinetics. How?



Regular & semilog graph of first order kinetics

- The half-life of a first order process is a constant & independent of initial concentration for a given drug, i.e, irrespective of initial drug concentration, the time required for initial concentration to decline by one-half remains the same. Thus, $\mathbf{t_{1/2}}$ of first-order process is vital PK parameter
- Most pharmacokinetic processes, ADME, follow first order kinetics

$$\mathbf{t_{1/2} = 0.693/K_1}$$

Linear Pharmacokinetics

- Change in plasma conc. due to ADME process is proportional to dose of drug administered (single or multiple)
- ADME processes follow First order kinetics

Eg: With a first-order elimination process, as the dose of drug increases, the plasma concentrations observed and AUC increase proportionally. That is, if the dose is doubled, plasma concentration and AUC also doubled

- No change in F, Ka, Ke, Vd, Clearance, $t_{1/2}$, etc. of most drugs when different doses are administered and/or when the drug is administered via different routes as a single dose or multiple doses

- Semilog plot for concentration versus time is super imposable (Principle of superimposition)
- Used to predict drug dosage

Example:

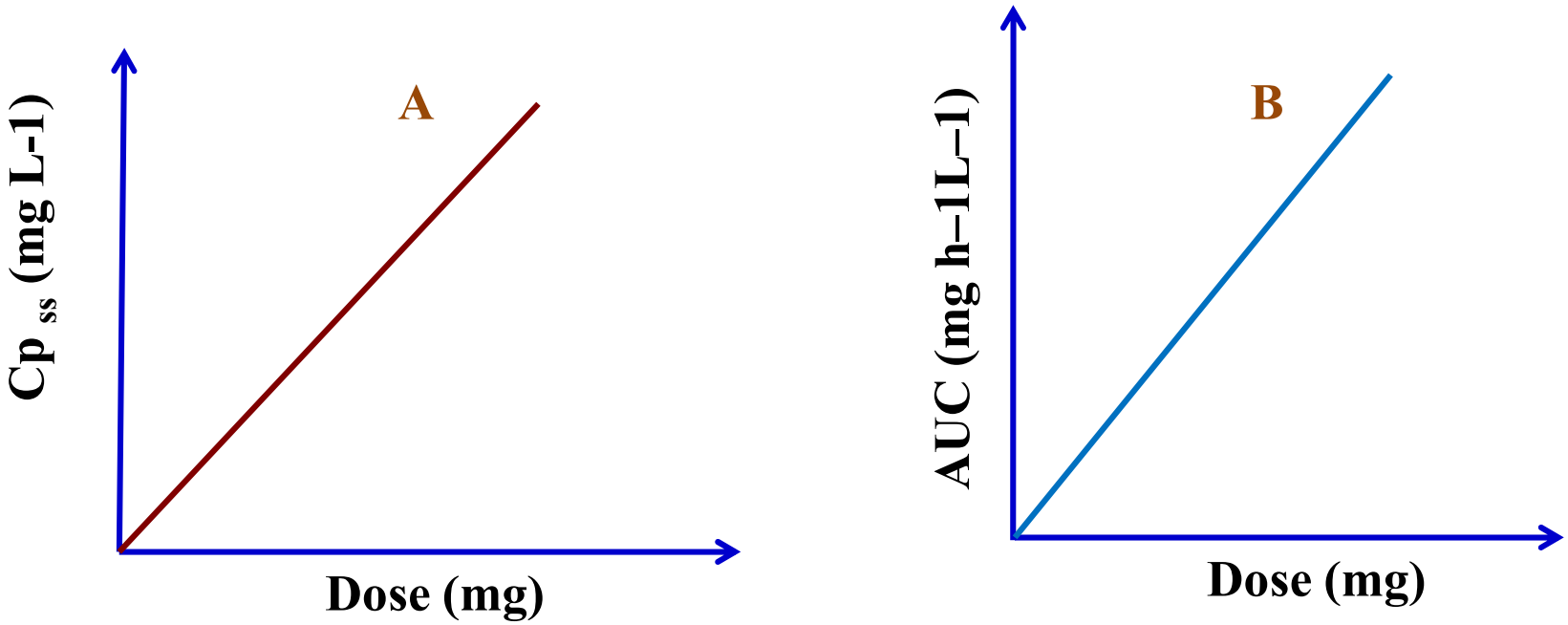
If a 100-mg daily dose of a drug produces a steady-state peak plasma concentration of 10 mg/L, we know that a 200-mg daily dose will result in a steady-state plasma concentration of 20 mg/L. (Note that *linear does not refer to the* plot of natural log of plasma concentration versus time)

Note: The principle of superposition assumes that early doses of drug never affect pharmacokinetics of subsequent doses

- Therefore, the blood levels after the second, third, or *n*th dose will overlay or superimpose the blood level attained after the $(n - 1)^{th}$ dose.

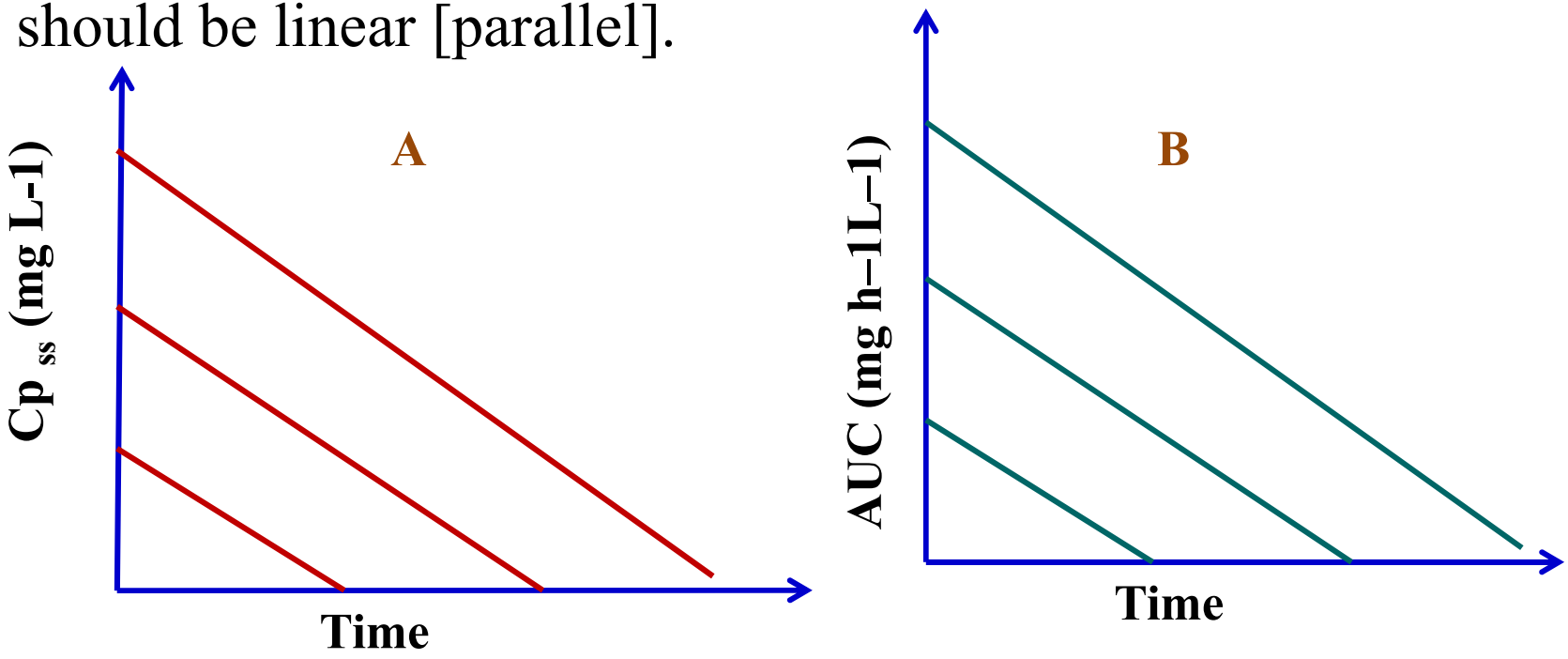
- In addition, the AUC $= \int_0^\infty Cpdt$ for the first dose is equal to the steady-state area between doses, ie, AUC = $\int_{t1}^{t2} Cpdt$

- Linearity simply means that both plasma concentration at a given time at steady state and the area under the plasma concentration versus time curve (AUC) are directly proportional to dose administered, as illustrated below:



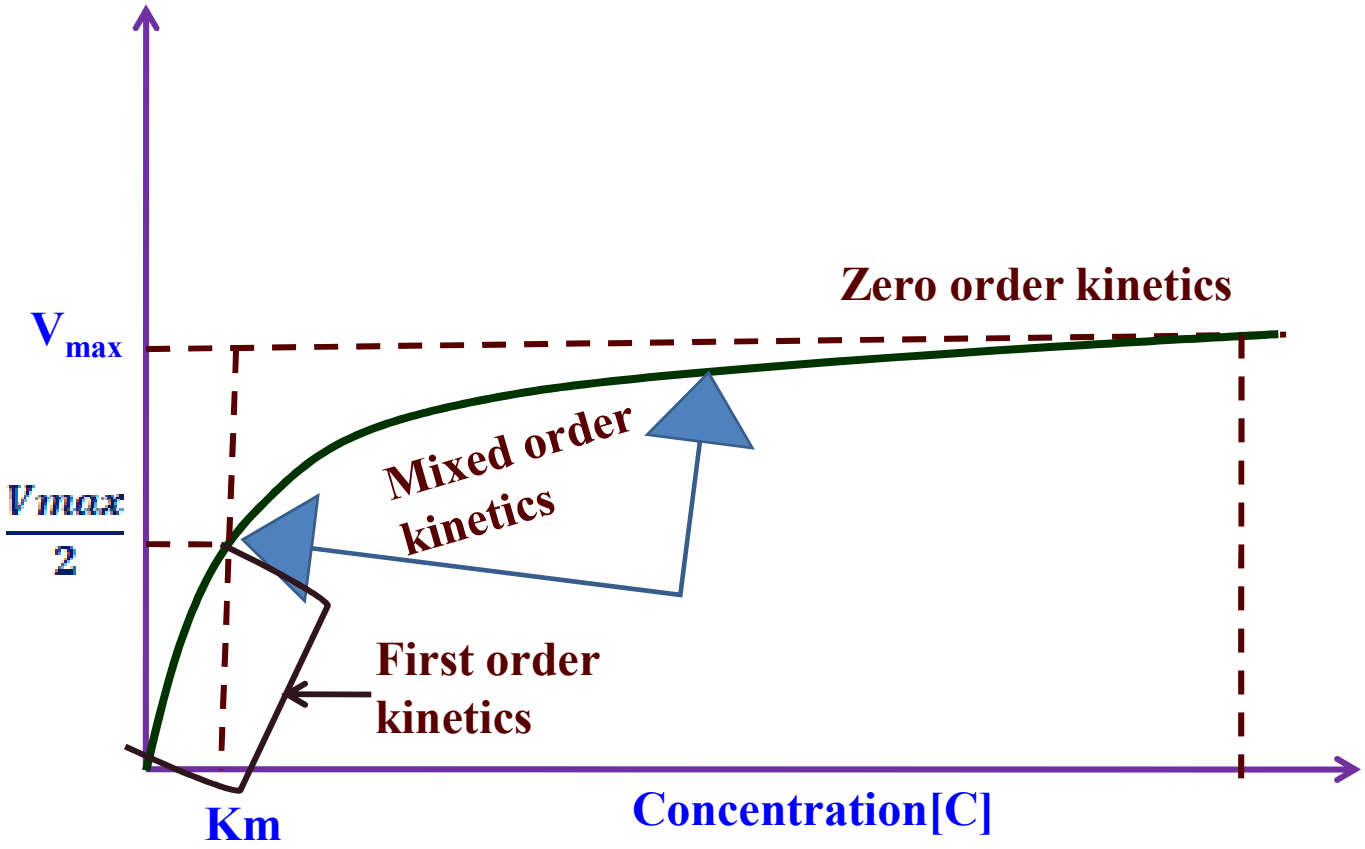
Relationship b/n plasma concentration (Cp) at a given time at steady state (A) and area under plasma concentration versus time curve (AUC) (B) against administered dose for a drug that exhibits dose-independent pharmacokinetics

- To determine if a drug is following dose-independent kinetics, the drug is given at various dosage levels and a plasma level vs time curve is obtained for each dose. The curves should exhibit parallel slopes if the drug follows dose-independent kinetics. Alternatively, a plot of areas under plasma level versus time curves at various doses should be linear [parallel].



Mixed order kinetics

- Kinetics of PK process for some drugs change from predominantly first order to predominantly zero-order with increasing dose or chronic medication, i.e, a mixture of both orders of kinetics is observed making the process a mixed-order kinetics
- At lower drug concentration, the rate process is linear, however, as drug dose increases or multiple doses of a drug are used deviation from linearity occurs making mixed order kinetics a nonlinear kinetics
- Mixed order kinetic is observed when PK process involves presence of substrate specific carriers or enzymes that have definite capacities [capacity limited] and get saturated at high drug concentration
- The kinetics of capacity limited processes is well explained by Michaelis-Menton kinetics



Graph of Michaelis-Menton kinetics

Elimination rate constant [Ke]

It is the ratio between rate of drug elimination and amount of drug in the body. Because as amount of drug in the body changes over time, the rate of drug elimination changes, but the elimination rate constant remains constant for first-order elimination. This makes it convenient to summarize drug elimination from the body independent of time or the amount of drug in the body. However, because it's difficult to measure the amount of drug in the body, D_B, it is preferred to convert drug amounts to drug concentrations in the body using the apparent volume of distribution.

Thus, elimination rate constant also describes the ratio between rate of change of drug concentration and drug concentration in the compartment

9.2. Basic pharmacokinetic models for drug absorption & disposition

Objectives of pharmacokinetics models

1. To understand assumptions associated with one compartment model
2. To understand properties of first order kinetics and linear models
3. To write differential equations for a simple pharmacokinetic model
4. To derive and use integrated equations for a one compartment linear model
5. To define, use, & calculate such parameters as K_e (elimination rate constant), $t_{1/2}$ (half-life), Cl (clearance), V_d (apparent volume of distribution) and AUC (area under the concentration versus time curve) as they apply to a **one compartment linear model**

Pharmacokinetics models refer to expressing mathematically or quantitatively time course of drug through out the body & computing meaningful pharmacokinetics parameters

Pharmacokinetic model is useful in:

- Characterizing the fate of drug in patient
- Predicting conc. of drug in various body fluids & tissue with dosage regimen
- having optimum dosage regimen for individual patient
- predicting possible accumulation of drugs &/or metabolites in the body of a patient
- Correlating drug concentration with pharmacological or toxicological activity
- Evaluating bioequivalence b/n different formulations
- Explaining drug interaction

Compartment models

There are different types of compartment models

Example

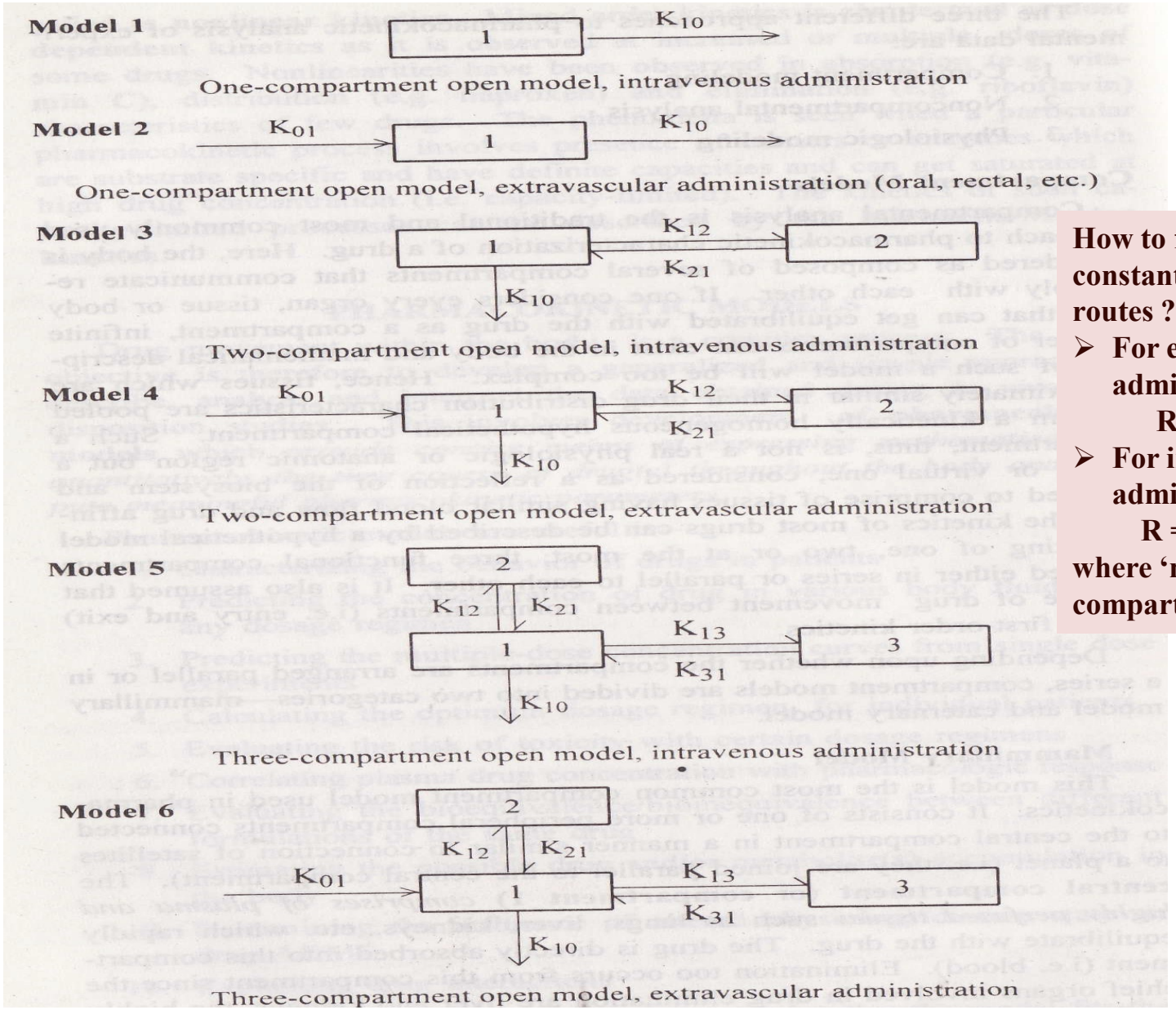
- One compartment model
- Two compartment model
- Three compartment model

“OPEN” and “CLOSED” models

- “Open model” :the administered drug dose is removed from body by an excretory mechanism (for most drugs kidneys are organs of excretion)
- If the drug is not removed from the body, then the model refers as “closed” model.

Which one is in existence?

Summary of different compartment open models



How to find number. of rate constant , R, for various routes ?

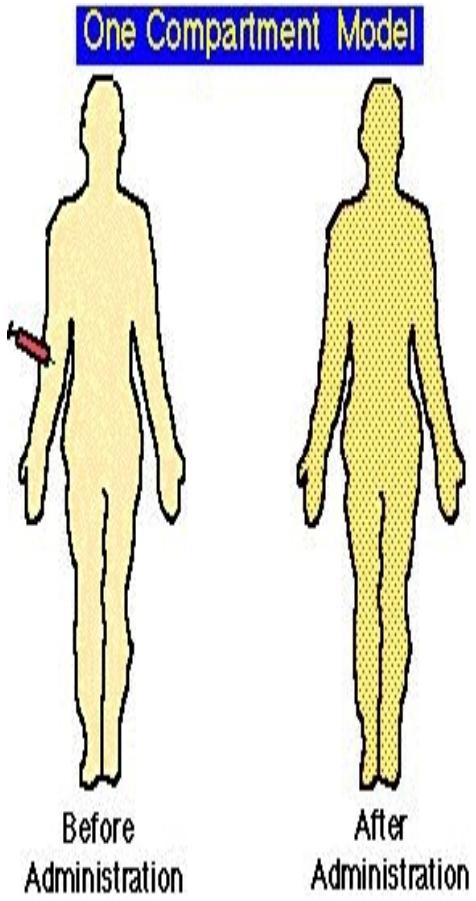
- **For extravascular administration,**
  R = 2n
- **For intravenous administration,**
  R = 2n -1

where 'n' is number of compartments

Assumptions of one compartment open model

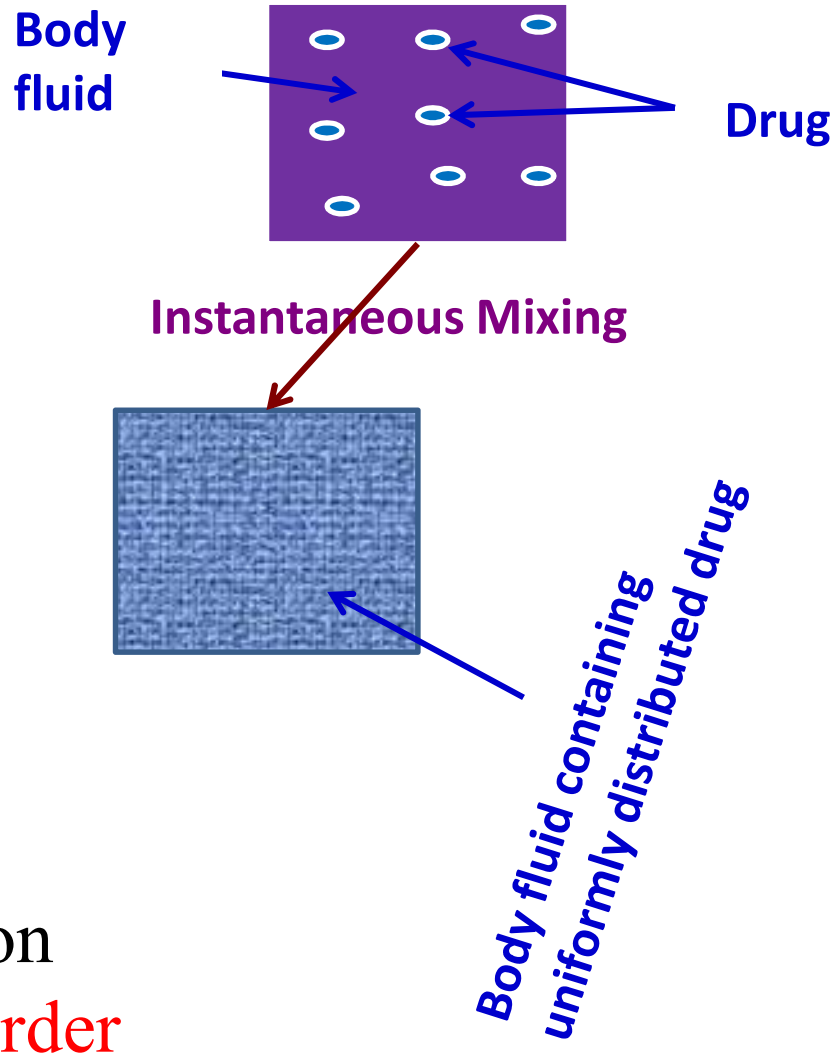
1. **Rapid equilibrium**

- Drug in the blood is in rapid equilibrium with drug in the extravasscular tissues
- This is not an exact representation due to difference in amount of blood supply to various tissues. However it is useful for a number of drugs to a reasonable approximation



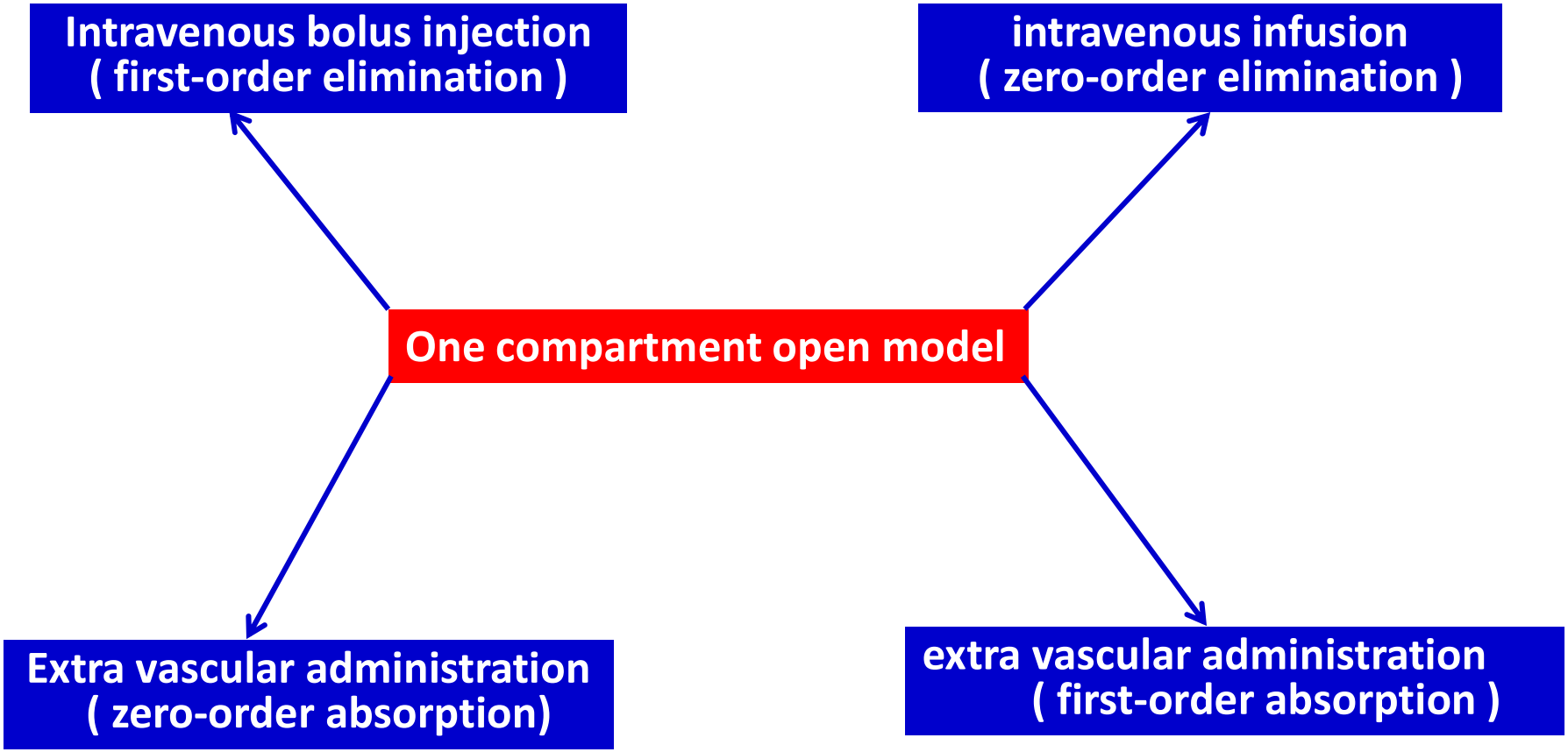
2. Rapid Mixing

Administered drug is assumed to be mixed instantaneously with blood or plasma



3. Linear Model

Assumes that drug elimination from the body follows first order kinetics


Intravenous bolus injection
(first-order elimination)
intravenous infusion
(zero-order elimination)
One compartment open model
Extra vascular administration
(zero-order absorption)
extra vascular administration
(first-order absorption)

Rate of drug presentation to body: IV bolus injection

$$dx/dt = \text{Rate in} - \text{Rate out}$$
$$= \text{drug availability} - \text{drug elimination}$$

- Since rate in or absorption is absent, rate of drug presentation to body becomes:

$$dx/dt = -\text{Rate out (or elimination)}$$

- If rate out or elimination follows first order kinetic, then:

$$dx/dt = -KeX \quad \ldots\ldots\ldots\ldots\ldots\ldots \text{Eq.1}$$

Where , Ke = rate constant out, X = Amount of drug

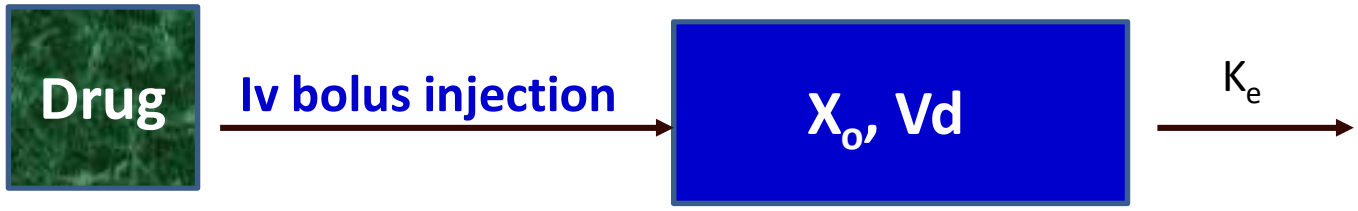
Various pharmacokinetic parameters can be computed if a drug is administered via **iv route**:

- Elimination phase
  - Elimination rate constant [Ke]
  - Elimination half life [$t_{1/2}$]
  - Clearance[Cl]
- Distribution phase
  - Apparent volume of distribution [Vd]

Elimination rate constant

- Rate of elimination for most drugs is a first-order process
- Elimination rate constant, K_E, is first –order elimination rate constant with units of $time^{-1}$, eg: hr^{-1}
- Active drug is generally removed from vascular compartment via metabolism &/or excretion
- Thus, $\mathbf{K_E = K_m + K_e}$, where $K_m + K_e$ are first order rate processes of metabolism & excretion, respectively

A. Schematic representation of one compartment model after rapid iv injection



B. Mathematical representation of drug after iv bolus

$$dx/dt = -k_E X \quad \ldots\ldots\ldots\

- Since it is difficult to directly determine amount of drug in body [i.e. X], we use relationship that exists between drug conc. in plasma [C] and X; as folllow:

$$X = V_d Cp \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\text{(eq. 5)}$$

Therefore, eq. 3 becomes, $Cp_t = Cp_o e^{-K_E t}$

- Subsequently , eq.4 becomes

$$\log Cp_t = \log Cp_o - k_E\, t/2.303 \quad \ldots\ldots\ldots\ldots\text{(eq.6a)}$$

$$\ln Cp_t = \ln Cp_o - k_E t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\text{(eq.6b)}$$

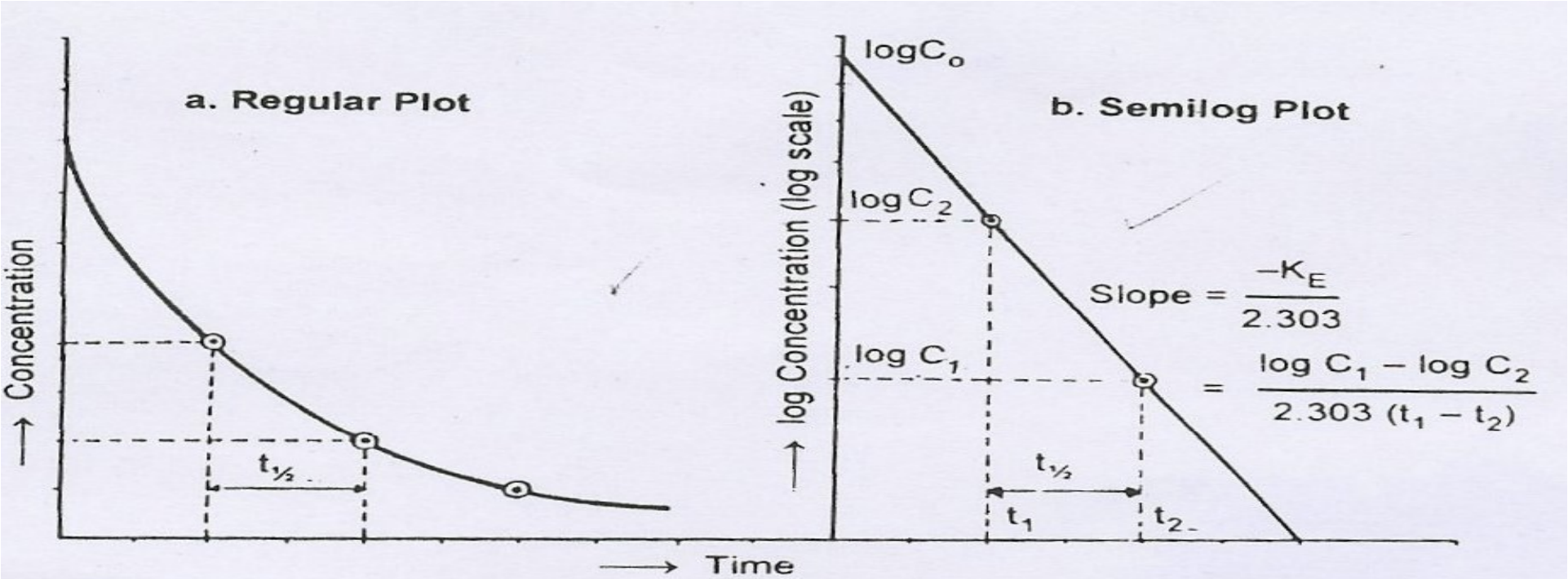


Fig. 10.2 (*a*) Cartesian plot of a drug that follows one-compartment kinetics and given by rapid i.v. injection, and (*b*) Semilogarithmic plot for the rate of elimination in a one-compartment model.

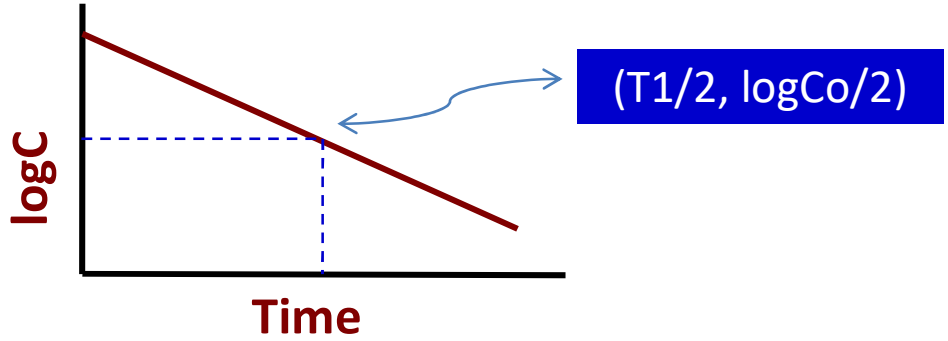
$$K_E = Ke + Km + Kb + Kl + \ldots \qquad \text{(eq.7)}$$

where K_E is overall elimination rate constant

Elimination half life : Can be computed as follow:

A. $t_{1/2} = \frac{0.693}{K_E}$ (eq.8)

B. Elimination half life can be readily obtained from the graph of logC Vs t



C. Half life is a secondary parameter that depends upon primary parameters such as clearance and volume of distribution. Or since $CL_T/Vd = K_E$

$$t_{1/2} = [0.693Vd]/Cl_T \quad \text{.....(eq.9)}$$

Apparent volume of distribution [Vd]

- Volume of fluid in w/h drug appears to be distributed.
  OR
- Volume of plasma in which the total amount of drug in the body would be required to be dissolved in order to reflect drug concentration attained in plasma

Note:

- Vd has no direct physiological or anatomical meaning
- Vd is not a 'real' volume but apparent volume of distribution

Note

- Assumes that drug concentration everywhere in the body is at equilibrium with that in plasma or serum
- Concentration of drug in plasma is not necessarily the same as in the liver, kidneys or other tissues. i.e., or
- Drug conc. in plasma does not equal to amount of drug in the kidney or amount of drug in the liver or amount of drug else where in tissues. Why ??
- However, changes in the drug concentration in plasma are directly proportional to changes in the amount of drug in the tissues i.e., Cp (plasma) $\propto$ X (tissues)

where ,$\propto$ stands for directly proportional

$$\frac{dx}{dt} = -Kex$$

$$\int_0^x dx = [x - 0] = x$$

Therefore, $X - KVd \int_0^\infty AUC$

However, $x = Vd.Cp$

$$\int_0^x dx = -KVd \int_0^\infty Cp.dt$$

$$\Rightarrow X = \text{KVd.AUC}$$

$$\Rightarrow Vd = \frac{x}{Ke.AUC}$$

However, $\int_0^\infty Cp.dt = \int_0^\infty AUC$

Therefore,

- For drugs given as i.v.bolus,

$$\mathbf{Vd} = \frac{\boldsymbol{Xo}}{\boldsymbol{Ke.AUC}}$$

- For drugs administered extravascularly,

$$\boldsymbol{Vd} - \frac{\boldsymbol{FXo}}{\boldsymbol{Ke.AUC}}$$

Where F=fraction of a drug that is absorbed and bioavailable

Significance of apparent volume of distribution

- For each drug ,the apparent Vd is constant
- Drugs with large apparent Vd are more concentrated extravascularly [EVF] than intrvascularly
- Drugs highly bound to plasma proteins have small Vd or
- Drugs that remain in vascular region has small Vd
- Pathologic cases that alter drug distribution can change Vd

Example

- Water soluble drugs have large Vd in edematous conditions since total body H_2O & total EVF increase
- Apparent Vd is affected by changes in the total body weight & lean body mass

Summary of fluid in the body		
Water Compartment	**Percent of body weight**	**Percent of total body water**
Plasma	4.5	7.5
Total Extracellular water	27	45
Total intracellular water	33	55
Total Body water	60	100

Illustration problems

A. A 50-kg woman was given a single IV dose of an antibacterial drug at a dose level of 6 mg/kg. Blood samples were taken at various time intervals. The concentration of the drug (*Cp) was determined in the* plasma fraction of each blood sample and the following data were obtained:

t (hr)	C_p *(μg/mL)*
0.25	8.21
0.5	7.87
1	7.23
3	5.15
6	3.09
9	1.11
12	0.4

Required

1. What are the values for Vd, ke, and $t_{1/2}$ for this drug?

2. This antibacterial agent is not effective at a plasma concentration of less than 2µg/ml. What is the duration of activity for this drug?

3. If the dose of the antibiotic were doubled exactly, what would be the increase in duration of activity?

4. How long would it take for 99.9% of this drug to be eliminated?

t (hr)	*C_p (µg/mL)*
0.25	8.21
0.5	7.87
1	7.23
3	5.15
6	3.09
9	1.11
12	0.4

B. New drug was given in a single intravenous dose of 200 mg to an 80-kg adult male patient. After 6 hours, the plasma drug concentration of drug was 1.5 mg/100 mL of plasma. Assuming that the apparent *Vd* is 10% of body weight:

1. Compute total amount of drug in the body fluids after 6 hours
2. What is the half-life of the new drug?

C. A new antibiotic drug was given in a single intravenous bolus of 4 mg/kg to five healthy male adults ranging in age from 23 to 38 years (average weight 75 kg). The pharmacokinetics of the plasma drug concentration "time curve for this drug fits a one-compartment model. The equation of the curve that best fits the data is: $Cp = 78e^{-0.46t}$

Required(assume units of µg/mL for *Cp and hr for t):*

1. What is the $t_{1/2}$? , *Vd?*
2. What is the plasma level of the drug after 4 hours?

3. Predict what body water compartment this drug might occupy and explain why you made this prediction

4. Assuming the drug is no longer effective when levels decline to less than 2µg/mL, when should you administer the next dose?

D. A drug has an elimination *t 1/2 of 6 hours and follows first-order kinetics. If a single 200-mg dose is given* to an adult male patient (68 kg) by IV bolus injection, what percent of the dose is lost in 24 hours?

E. If the amount of drug in the body declines from 100% of the dose (IV bolus injection) to 25% of the dose in 8 hours, what is the elimination half-life for this drug? (Assume first-order kinetics.)

F. A drug has an elimination half-life of 8 hours and follows first-order elimination kinetics. If a single 600 mg dose is given to an adult female patient (62 kg) by rapid IV injection.

1. what percent of the dose is eliminated (lost) in 24 hours assuming the apparent *Vd is 400 mL/kg?*
2. *What is the expected plasma drug* concentration (*C p) at 24 hours postdose?*

G. For drugs that follow a one-compartment open model kinetics, do you think the tissues and plasma must have the same drug concentration? Why?

H. If a patient has a potentially toxic Digoxin level of 4.5g/L & half-life of Digoxin in this patient is 60 h,

i. Calculate elimination rate constant

ii. For how long should the drug be stopped to allow the level to fall to 1.5g/L?

[Hint :Assume renal function is stable& absorption is complete]

One compartment open model: Extravascular administration

Drug absorption is a prerequisite for its therapeutic effectiveness if given extravascularly

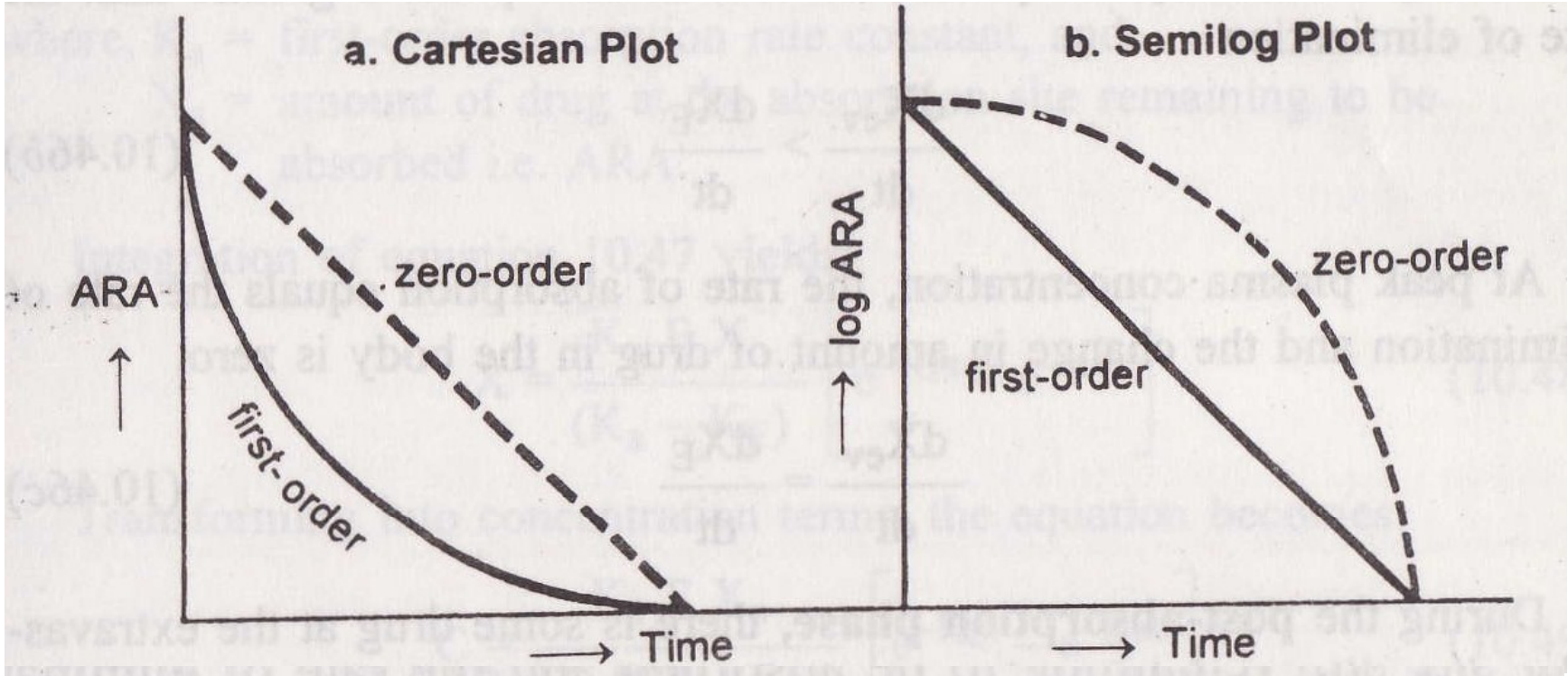
The rate of absorption can be zero-order or first-order process depending on the nature of the administered drug

Zero-order extravascular [extv] drug absorption

- Characterized by a constant rate of absorption
- It is independent of amount of drug remaining to be absorbed[ARA]
- Its regular ARA versus time plot is linear with slope equal to rate of absorption

First-order extravascular [extv] drug absorption

- Characterized by variable rate of drug absorption i.e., rate of absorption decline with a decrease in ARA & vice versa
- Its regular ARA versus time plot is curvilinear and semilog plot is straight line with slope equal to absorption rate constant

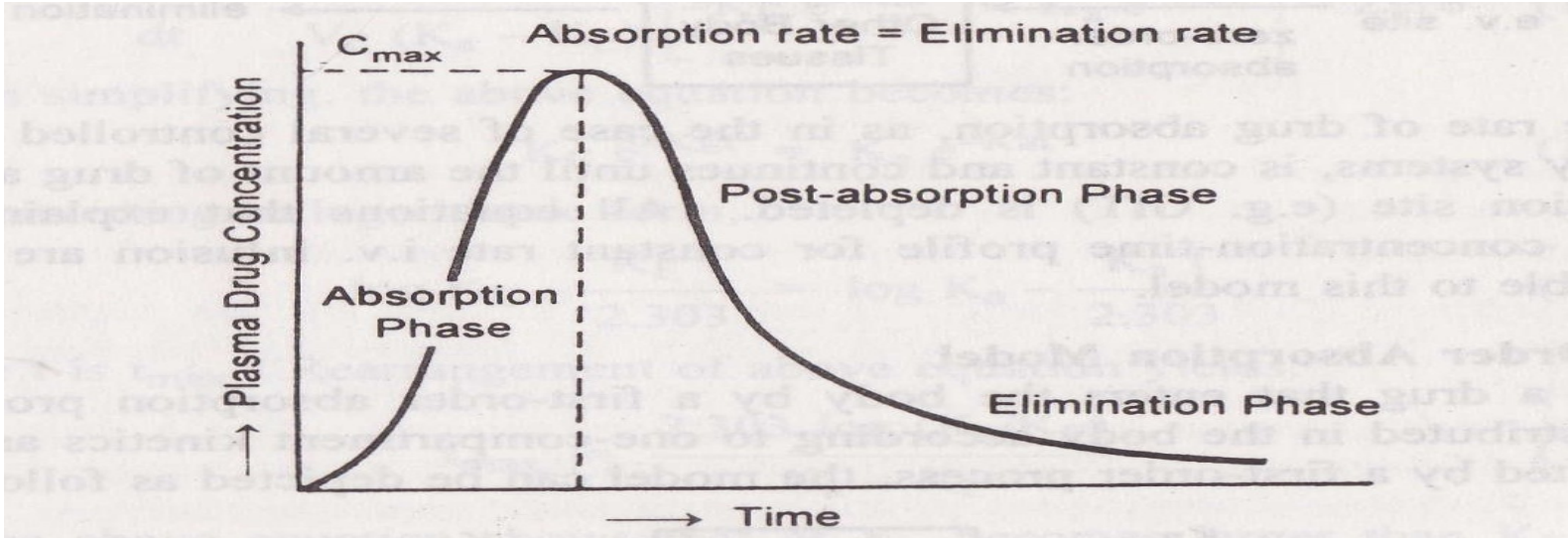


Distinction between zero-order and first-order absorption processes. *Figure a* is regular plot, and *Figure b* a semilog plot of amount of drug remaining to be absorbed (ARA) versus time t.

After extravascular Administration, rate of change in the amount of drug in the body, dx/d_t is the difference between rate of absorption dX_{exv}/d_t & rate of elimination dX_E/d_t.

dx/d_t = Rate of absorption – Rate of elimination

$dx/d_t = dX_{exv}/d_t - dX_E/d_t$



The absorption and elimination phases of the plasma concentration-time profile obtained after extravascular administration of a single dose of a drug.

For a drug that follows one-compartment kinetics, plasma concentration-time profile is characterized by absorption phase, post-absorption phase and elimination phase

During absorption phase, rate of absorption is greater than rate of elimination

$$dX_{exv}/d_t > dX_E/d_t$$

At peak plasma concentration, rate of absorption is equal to rate of elimination & change in the amount of drug in the body is zero

$$dX_{exv}/d_t = dX_E/d_t$$

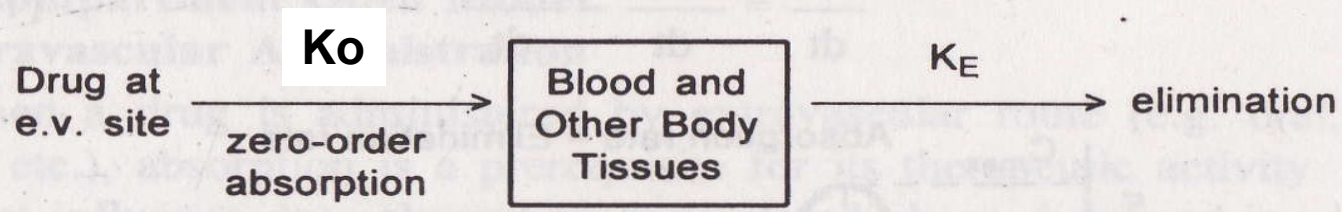
During the post-absorption phase, there is some drug at the extravascular site still remaining to be absorbed & the rate of absorption is less than the rate of elimination

$$dX_{exv}/d_t < dX_E/d_t$$

After completion of drug absorption, its rate becomes zero & plasma level time curve is characterized only by elimination phase

Zero-Order Absorption Model

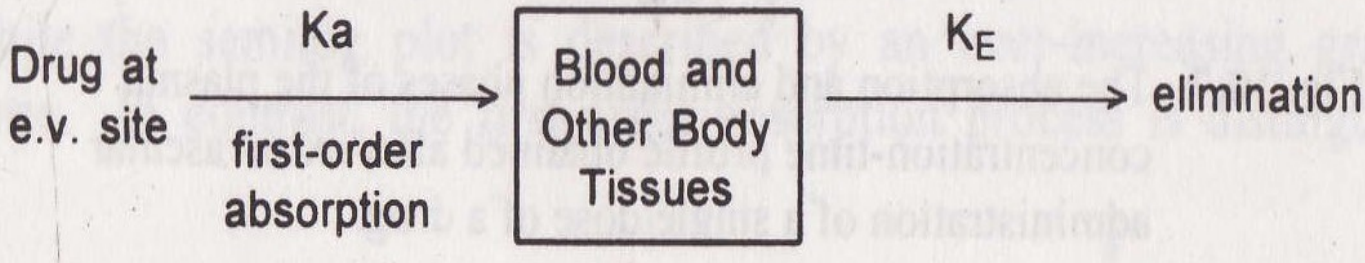
This model is similar to that for constant rate infusion.



The rate of drug absorption, as in the case of several controlled drug delivery systems, is constant and continues until the amount of drug at the absorption site (e.g. GIT) is depleted. All equations that explain the plasma concentration-time profile for constant rate i.v. infusion are also applicable to this model.

First-Order Absorption Model

For a drug that enters the body by a first-order absorption process, gets distributed in the body according to one-compartment kinetics and is eliminated by a first-order process, the model can be depicted as follows:



The differential form of equation:

$$dx/d_t = dX_{exv}/d_t - dX_E/d_t \text{ is given by :}$$

$$dx/d_t = K_aX_a - K_EX \text{ , where}$$

'K'$_a$ is first order absorption rate constant & 'X'$_a$ drug amount remaining to be absorbed at absorption site.

After integration of the above equation, we have:

$$X = K_aFX_0 [e^{-K_E t} - e^{-Kat}]/ [K_a - K_E]$$

Transforming into concentration terms, the equation becomes:

$$X/V_d = K_aFX_0 [e^{-K_E t} - e^{-Kat}]/ V_d [K_a - K_E]$$

$$C = K_aFC_0 [e^{-K_E t} - e^{-Kat}]/ [K_a - K_E]$$

F = fraction of drug absorbed systemically after extravascular administration

At peak plasma drug concentration, $K_aX_a = K_EX$ & Rate of change in plasma drug concentration dc/dt =0

This rate is obtained by differentiating the equation

$$\mathbf{C = K_aFX_0\,[e^{-K_E t} - e^{-Kat}]/\,V_dK_a - K_E}$$

which gives

$$\mathbf{dC/dt = K_aFX_0\,[-KEe^{-K_E t} + Ka\,e^{-Kat}]/\,V_dK_a - K_E = 0}$$

On simplifying, the above equation becomes:

$$\mathbf{K_Ee^{-K_E t} = K_a\,e^{-Kat}}$$

Converting to logarithmic form,

$$\mathbf{\log K_E - K_E t\,/2.303 = \log K_a - K_a t\,/2.303}$$

where 't' is t_{max} , rearrangement of the equation yields:

$$\mathbf{t_{max} = \underline{2.303\log(K_a/K_E)/K_a - K_E}}$$

Note: As 'K'_a becomes larger than 'K'_E, t_{max} becomes smaller since $(K_a - K_E)$ increases much faster than $\log(K_a/K_E)$

C_{max} can be computed from:

$$\mathbf{C_{max} = FX_0 [e^{-K_E t_{max}}]/ V_d}$$

It has been shown that at C_{max}, when $K_a = K_E$, $\mathbf{t_{max} = 1/ K_E}$, then $C_{max} = FX_0 [e^{-K_E t_{max}}]/ V_d$ becomes

$$\mathbf{C_{max} = [FX_0 e^{-1}]/V_d}$$

$$\mathbf{= \underline{0.37 [FX_0]/V_d = 0.37C_0}}$$

Note:

$[FX_0]/V_d$ represents C_0 following i.v.bolus. Therefore, the maximum attainable plasma drug concentration after extravascular administration is just 37% of the maximum level attainable with intravascular bolus in the same dose.

Examples-1

If Viomycin plasma concentration after I.V. Bolus administration was 10.0 & 5.5 μg/ml at 2 & 4 hour, respectively, assuming one-compartment kinetics, calculate:

a. Half-life of the drug
b. Plasma drug concentration at time zero
c. Apparent volume of distribution if administered dose was 300 mg
d. Find t_{max} & C_{max} if same drug was administered through extravascular route

Exercise

If the equation that best fits plasma level time curve of azlocilin after an i.v. Bolus dose of 2000mg, assuming one compartment kinetics is $C=143e^{-0.87t}$, answer the following questions if 't' is in hr & 'C' is in µg/ml.

1. What is the apparent Vd?
2. What is the elimination $t_{1/2}$ of the drug
3. What will be the plasma drug concentration after 6 hours
4. How much of the drug will be left in the body after 6 hours?

5. When should the next dose be administered if the drug becomes ineffective when the plasma level falls below 50 µg/ml ?
6. What will be the therapeutic index of the drug if the therapeutic range is 50 to 500µg/ml ?
7. How much dose should be administered to attain an instantaneous plasma concentration of 500µg/ml
8. For how long will the plasma level lie in the therapeutic window if the above dose is given as i.v. Bolus?

Practice problems

1. The half-life of propranolol in a 60 kg patient is 4 hours & V_d is 5.5 liter/kg.

Answer the following questions:

a. Determine total systemic clearance of the drug

b. What will be its renal clearance if fraction excreted unchanged in urine is 0.047?

2. What is the influence of K_a & K_e on C_{max}, T_{max} & AUC?

3. A single 500 mg IV bolus injection of cefamandole nafate (Mandol, Lilly) is given to an adult female patient (63 years, 55 kg) for a septicemic infection. The apparent volume of distribution is 0.1 L/kg and the elimination half-life is 0.75 hour. Assuming the drug is eliminated by first-order kinetics & described by a one-compartment model, calculate the following:

a. Initial plasma drug concentration

b. The amount of drug in the body 4 hours after the dose is given

c. The time for the drug to decline to 0.5μg/mL, the minimum inhibitory concentration for streptococci.

4. A drug has an elimination half-life of 8 hours and follows first-order elimination kinetics. A single 600-mg dose is given to an adult female patient (62 kg) by rapid IV injection.

Answer the following questions

a. what percent of the dose is eliminated (lost) in 24 hours assuming the apparent Vd is 400 mL/kg?

b. What is the expected plasma drug concentration (Cp) at 24 hours postdose?

5. What is the difference between a rate and a rate constant? Explain using arbitrary examples

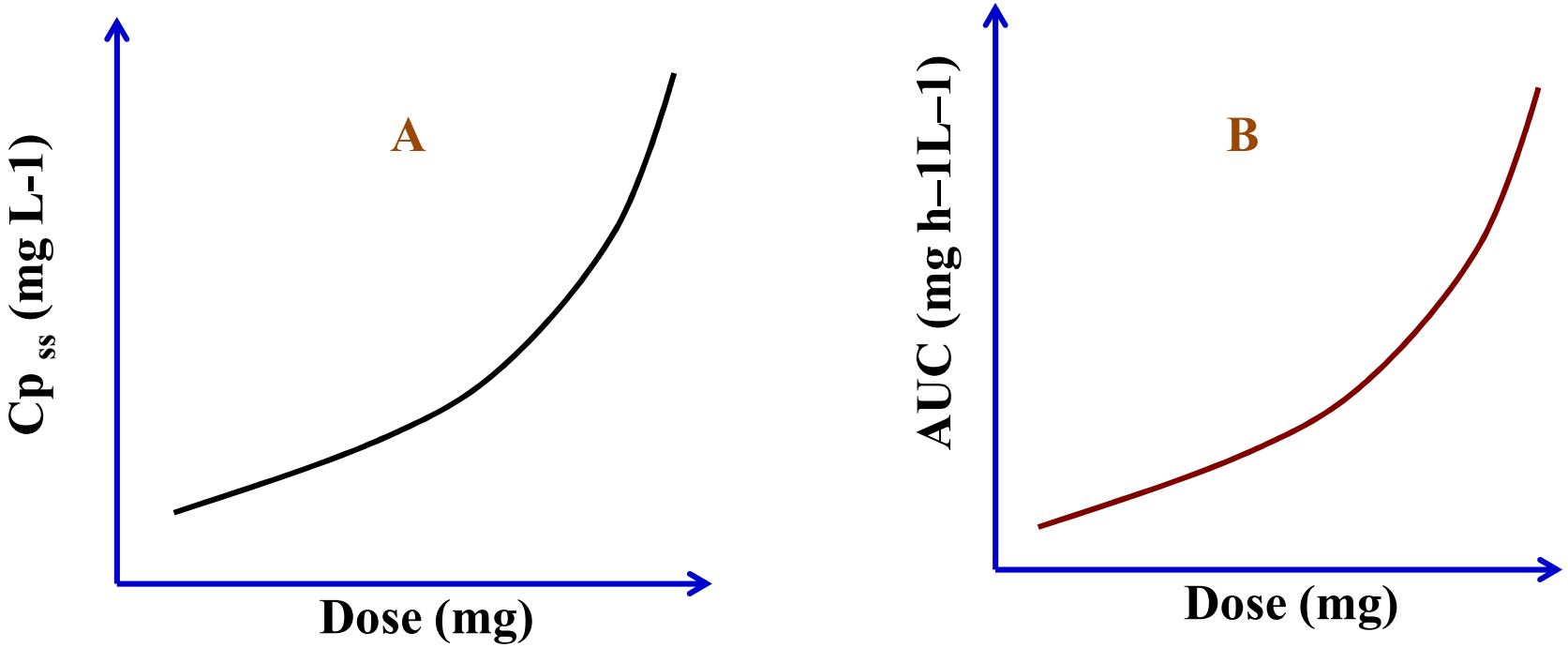
6. A drug has an elimination $t_{1/2}$ of 6 hours and follows first-order kinetics. If a single 200-mg dose is given to an adult male patient (68 kg) by IV bolus injection, what percent of the dose is lost in 24 hours?

7. A 70-kg volunteer is given an intravenous dose of an antibiotic. The serum drug concentrations were 1.2 and 0.3 mg/mL as determined at 2 hours and 5 hours following drug administration, respectively. What is the biologic half-life for this drug, assuming first-order elimination kinetics?

10. Nonlinear pharmacokinetics

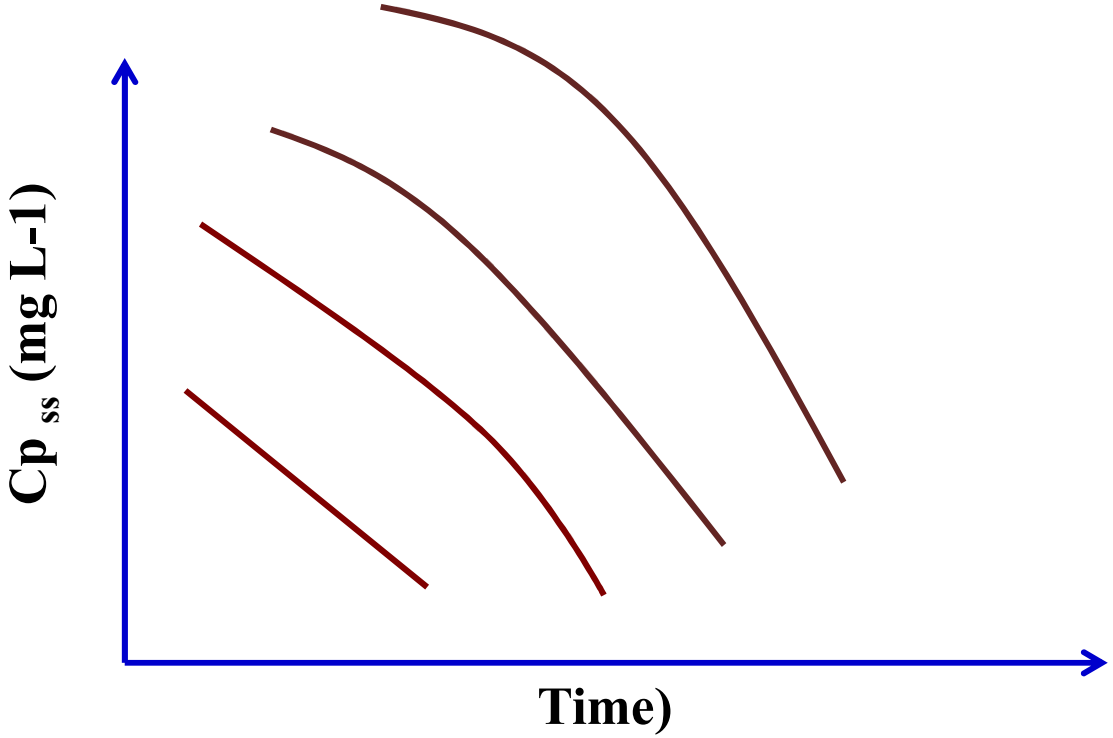
Nonlinear Pharmacokinetics

- Rate process of ADME are dependent on **carrier** or **enzymes** having definite capacity & hence subjected to saturation
- Change in concentration is no more proportional to dose administered during the total ADME process
- For drugs exhibiting nonlinear or dose dependent kinetics **clearance, Vd & elimination half life** may vary depending on the administered dose. Because one or more of kinetic processes (absorption, distribution &/or elimination) of the drug may follow First order + Zero order kinetics. Thus, the r/ship b/n AUC or the plasma concentration at a given time at steady state & the administered dose is not linear [Fig. A & B]



Relationship b/n plasma concentration (Cp) at a given time at steady state (A) and area under plasma concentration versus time curve (AUC) (B) against administered dose for a drug that exhibits dose-dependent pharmacokinetics

- Furthermore, administration of different doses of these drugs may not result in parallel Cp versus time profiles expected for drugs with linear pharmacokinetics, as shown below.



The relationship between plasma concentration (Cp) and time following administration of different doses of a drug that exhibits dose-dependent elimination pharmacokinetics

Comparison of Linear & nonlinear pharmacokinetics	
Linear Pharmacokinetics	**Non Linear Pharmacokinetics**
Pharmacokinetic parameters for a drug would not change with change in dose	Pharmacokinetic parameters for a drug can change with change in dose
Dose Independent	Dose dependent
First Order kinetics	Mixed order, Saturated kinetics, capacity limited
All semilog plots of C vs t for different doses are superimposable	All semilog plots of Conc. versus time for different doses are not superimposable

Types of PK	Causes	Examples
Gastrointestinal absorption	Absorption is carrier mediated	Riboflavin, gebapentin, Ldopa, baclofen, ceftibuten
	Drugs with low solubility in GI but relatively high dose	Chorothiazide, griseofulvin, danazol
	Presystemic hepatic metabolism attains saturation	Propranolol, hydralazine
Distribution	Saturable plasma protein binding	Phenylbutazone , disopyramide, lidocaine, ceftriaxone, salicylic acid, Phenytoin, warfarin
	Cellular uptake	Methicillin (rabbit)
	Tissue binding	Imiprimine (rat)
	Saturable transport into or out of tissues	Methotrexate

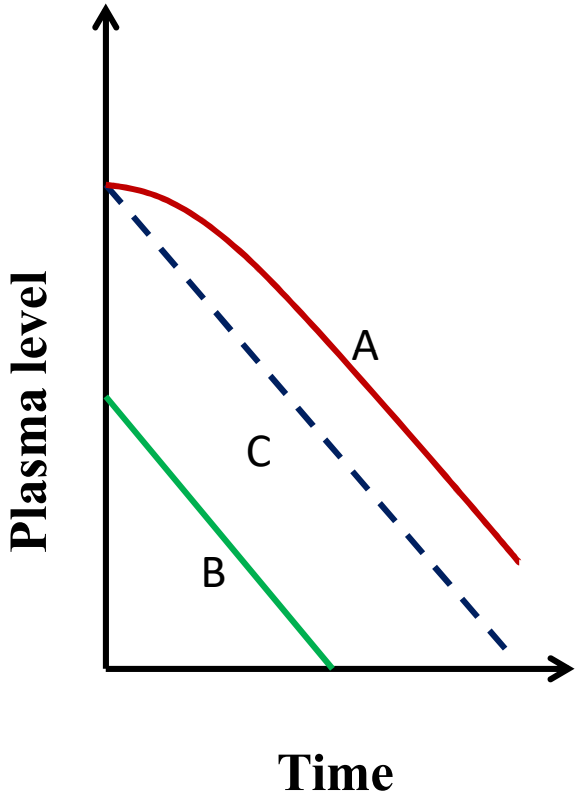
Types of PK	Causes	Examples
Renal excretion	Active secretion	Mezlocillin, paraaminohippuric acid, dicloxacillin,
	Tubular reabsorption	Riboflavin, ascorbic acid
	Change in urine pH	Salicylic acid, dextroamphetamine
Metabolism	Saturable metabolism	Phenytoin, Salicyclic acid, Alcohol, theophylline, Valproic acid
	Cofactor or enzyme limitation	Acetaminophen, alcohol
	Altered hepatic blood flow	Propranolol, verapamil
	Metabolite inhibition	Diazepam
Bilary excretion	Biliary secretion	Iodipamide, sulfobromophthalein sodium
	Enterohepatic recycling	Cimetidine, isotretinoin

Characteristics of drugs demonstrating saturation kinetics

1. Elimination of drug does not follow simple first-order kinetics—that is, elimination kinetics are nonlinear
2. Elimination half-life changes as dose is increased
3. Usually, the elimination half-life increases with increased dose due to saturation of enzyme system. However, elimination half-life might decrease due to "self"-induction of liver biotransformation enzymes, as is observed for carbamazepine

4. AUC is not proportional to amount of bioavailable drug
5. The saturation of capacity-limited processes may be affected by other drugs that require the same enzyme or carrier-mediated system (ie, competition effects).
6. The composition and/or ratio of the metabolites of a drug may be affected by a change in the dose, as shown below

- **Small dose** indicates apparent first order kinetics because no saturation kinetics occur **(curve *B*)**
- **Large dose :** Initial slow elimination phase followed by much more rapid elimination at lower blood conc.**[curve A]**
- If pharmacokinetic data were estimated only from blood levels described by curve B, then a twofold increase in dose would give blood profile presented in **(curve C),** which considerably underestimates drug concentration & duration of action



Capacity-limited metabolism

- Known as saturable metabolism, Michaelis–Menten kinetics, or mixed order kinetics
- The process of enzymatic metabolism of drugs may be explained by the relationship depicted below:

  Enzyme + drug → Enzyme–drug complex → Enzyme + Metabolite

- According to the principles of Michaelis–Menten kinetics, the rate of drug metabolism changes as a function of drug concentration

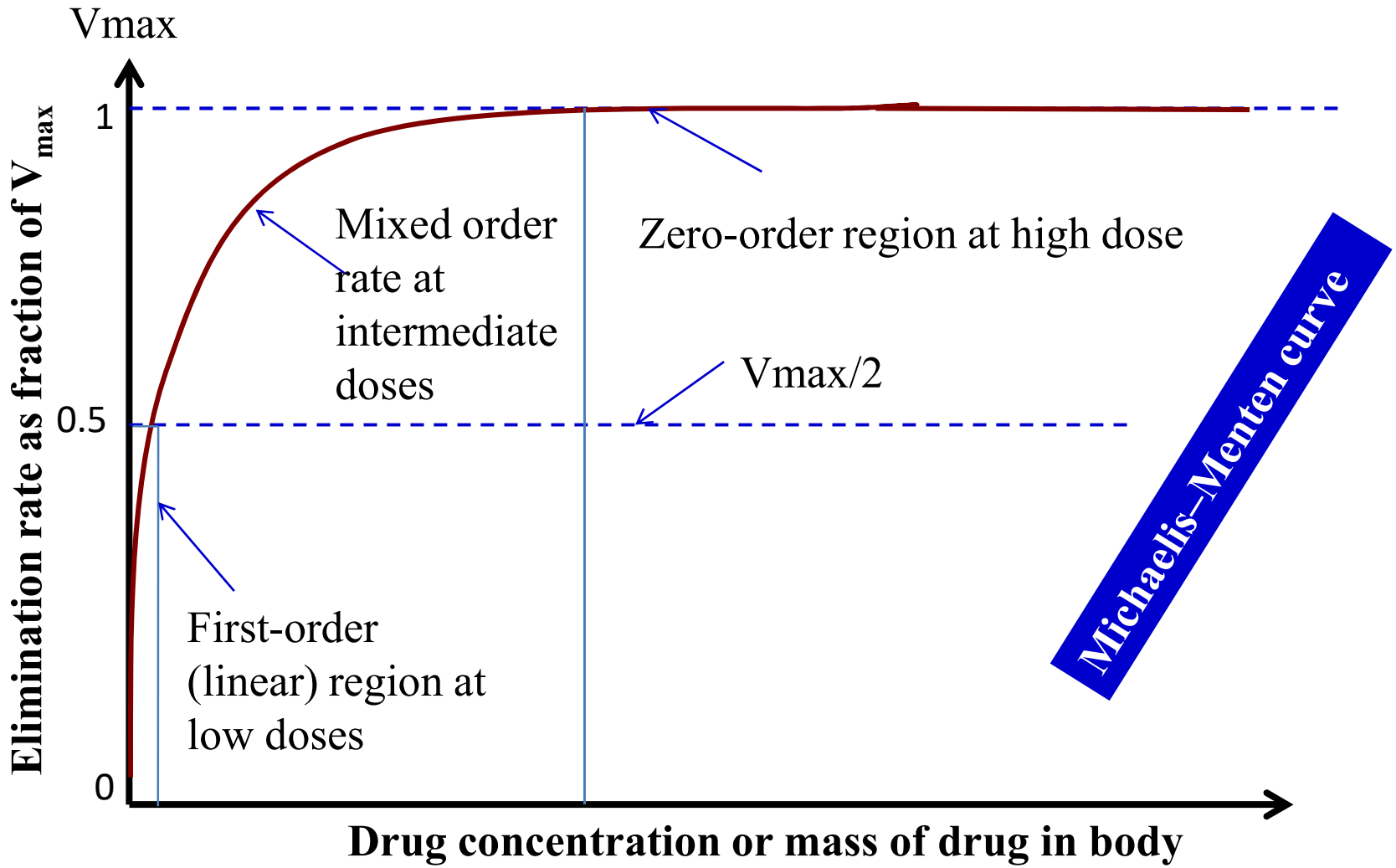
Michaelis–Menten kinetics:

$$\text{Elimination rate} = \frac{dC_p}{dt} = \frac{V_{max} C_p}{K_m + C_p}$$,where

- dCp/dt = rate of decline of drug conc. with time,
- V_{max} = Theoretical maximum rate of the process,
- K_m =It is equal to drug concentration or amount of drug in the body at $0.5V_{max}$. It is Michaelis constant, reflecting **capacity of the** enzyme system

Note: Km is inversely related to affinity of drug for metabolizing enzymes (the higher the affinity, the lower the Km value).

C p >> K m	C p = K m	C p <<K m
Saturation of enzymes occurs	Rate of metabolic process is equal to one half of its max. rate $-dc/dt = V_{max}/2$	rate of drug elimination becomes a first-order process
Value for K_M *is* negligible		$-\frac{dC_p}{dt} = \frac{V_{max}C_p}{C_p + K_M} = \frac{V_{max}}{K_M}C_p$ $-\frac{dC_p}{dt} = k'C_p$
Elimination rate proceeds at constant rate $-\frac{dC_p}{dt} = \frac{V_{max}C_p}{C_p} = V_{max}$		



Relationship between elimination rate and the plasma concentration of a drug that exhibits dose-dependent pharmacokinetics. At high drug concentrations, where saturation occurs, the elimination rate approaches its maximum, Vmax.

Practice Problems

1. Assuming for a drug V_{max} = 0.5 µg/ml per hour, K_M = 0.1µ g/ml, how long would it take for the plasma drug concentration to decrease from 20 to 12 µg/mL?

Solution

- Because 12 µg/ml is above the saturable level, i.e, 0.1 µg/ml, elimination occurs at a zero-order rate of approximately 0.5 µg/ml per hour.
- Time needed for plasma drug conc. to reach 12 µg/ml is given by:

$$t = [Co - Ct]/Vmax = [20 - 12]/ 0.5 \text{ µg/ml per hour}$$

$$= 8/0.5 \text{ per hr} = \underline{16 \text{ hrs}}$$

Drug Conc. (*C p) (g/mL)*	Elimination Rate (g/mL per hr)	Elimination Rate constant =ratio of elimination rate to drug conc.
0.01	0.011	1.1
0.02	0.022	1.1
0.03	0.033	1.1
0.04	0.043	1.1
0.05	0.053	1.1

2. If a drug has km = 0.8 mg/ml, Vmax =0.9 mg/ml/hr and Cp ≤ 0.05µg/ml as shown in the table.

a. Find ratio of elimination rate to drug conc.

b. Find k_E' based on saturation kinetics

c. What does the above results shows?

d. How long would it take for plasma drug conc. to decline from 0.05 to 0.005 g/mL based on the above assumptions?

Note: **Enzymatic drug elimination can change from a nonlinear to a linear process over a restricted conc. range. This is evident because the rate constant (or elimination rate/drug conc.) values are constant. i.e., at drug concentrations below 0.05 g/ml, the ratio of elimination rate to drug concentration has a constant value of 1.1/ hr. Mathematically, when Cp is much smaller than KM, Cp in the denominator is negligible & elimination rate becomes first order kinetics**

Note

- When given in therapeutic doses, most drugs produce plasma drug concentrations well below K_M *for all* carrier-mediated enzyme systems affecting drug's ADME
- Therefore, most drugs at normal therapeutic concentrations follow first-order rate processes.
- Only a few drugs, such as salicylate and phenytoin,[or WATT Power] tend to saturate hepatic mixed-function oxidases at higher therapeutic doses. With these drugs, elimination kinetics are first-order with very small doses, mixed order at higher doses, and may approach zero-order with very high therapeutic doses

3. After a single 400-mg dose is given by IV bolus injection, the drug is distributed into a single compartment and is eliminated by capacity-limited pharmacokinetics.

Compute the time for a drug to decline from 400 to 20 mg assuming:

a. V_{max} of the drug is 200 mg/hr & Km is 38 mg/L

b. V_{max} of the drug is 100 mg/hr & Km is 38 mg/L

c. Discuss on the relationship between time & V_{max}

d. Km & V_{max} of the drug are 76 mg/L & 200 mg/hr, respectively

e. Discuss on the relationship between time & Km

Clearance

- Drug clearance (CL) is defined as volume of plasma in vascular compartment cleared of drug per unit time by processes of metabolism &/or excretion
- Clearance for a drug is constant if the drug is eliminated by first-order kinetics
- Drug can be cleared by renal excretion or by metabolism or both plus by other routes

Clearance[Cl] = [rate of elimination] / plasma [drug] Or

$$Cl = KeV_d = \frac{d[\text{Amount of drug in the body}]/dt}{Db/Vd} = \frac{\text{Rate of drug elimination}}{Db/Vd} = \frac{dD^0b/dt}{Cp}$$

Therefore,

- Renal clearance [$\mathbf{Cl_R}$] = rate of elimination by kidney/Cp
- Hepatic clearance [$\mathbf{Cl_H}$] = rate of elimination by liver/Cp
- Other organ clearance [$\mathbf{Cl_{other}}$] =

  rate of elimination by other organ/Cp

❖ Total body clearance:

$$\mathbf{Cl_T = Cl_R + Cl_H + Cl_{other}}$$

= Renal clearance + non-renal clearance

- According to earlier definition

  Cl = (dx /dt) / [C] , Substituting eq.1 , i.e: $dx/dt = K_E X$, in to above eq ,we have

$$Cl_t = (K_E X)/ C \qquad \text{(eq 15)}$$

- By incorporating equation 15 and equation for vol. of dist. (Vd= X/C), We can get

$$Cl_t = K_E Vd \qquad \text{(eq.16)}$$

For drugs given as intravenous bolus, $\mathbf{CL_t = X_o/AUC}$ and

For drugs given extravascularly, $\mathbf{CL_t = FX_o/AUC}$

Example

1.If a drug has a CL of 2L/h, then 2 litres of the Vd is cleared of drug per hour

2. If the Cp for same drug is 10 mg/L, then 20 mg of drug is cleared per hour

- Parallel equations can be written for renal and hepatic clearance.

$$Cl_H = Km\ Vd \ldots\ldots\ldots \quad \text{(eq.17)}$$

$$Cl_R = Ke\ Vd \ldots\ldots\ldots \quad \text{(eq.18)}$$

$Cl_H + Cl_R = Km\ Vd + Ke\ Vd = Vd\ [Km + Ke] = Vd\ K_E$

but $K_E = 0.693/t_{1/2}$ →substituting in for K_E

we have , $Cl_t = 0.693\ Vd/\ t_{1/2}$ ……(eq.19)

Note: $Km + Ke + K_{others} = K_E$

$$\%\ \text{drug metabolized} = \frac{K_m}{K_E} = \frac{\text{Total metabolite excreted in urine}}{\text{Total dose absorbed}} = \frac{D^{\infty}_u}{FD_o}$$

$$\%\ \text{drug excreted} = \frac{K_e}{K_E} = \frac{\text{Total drug excreted in urine}}{\text{Total dose absorbed}} = \frac{D^{\infty}_u}{FD_o}$$

Summary on clearance

- Ability of organs of elimination (*e.g.* kidney, liver) to "clear" drug from the bloodstream
- Volume of fluid ,completely cleared of drug per unit time
- Pharmacokinetic term used in determination of maintenance doses
- Volume of blood in a defined region of the body that is cleared of a drug in a unit time [L/hr or L/hr/kg]
- Clearance is a more useful concept in reality than $t_{1/2}$ or k_{el} since it takes into account blood flow rate
- Clearance varies with body weight &/or degree of Plasma protein binding.

Examples

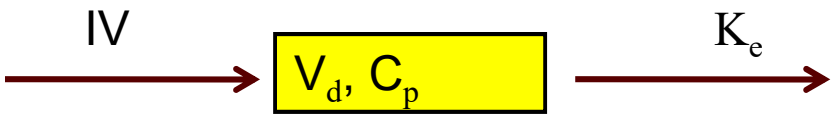
1. Determine total body clearance for a drug in a 70-kg male patient. The drug follows kinetics of a one-compartment model and has an elimination half-life of 3 hours with an apparent volume of distribution of 100 mL/kg.
2. Penicillin has a Cl of 15 mL/min. Calculate elimination rate for penicillin when the plasma drug concentration, Cp, is 2 mg/mL.
3. Using the previous penicillin example, assume that the plasma penicillin concentration is 10 mg/mL. Determine the rate of drug elimination.
4. How could you realate elimination rate of penicilin with its plasma concentration?

5. Assume that 100 mg of the drug was administered to a patient and the drug was completely absorbed (F = 1). A complete (cumulative) urine collection was obtained disclosing amount of metabolite-A 10mg, metabolite-B 20mg and unchanged drug 70 mg. The overall elimination half-life & elimination rate constant for the drug were 2.0 hours & 0.347 h^{-1}, respectively.

a. Determine renal excretion rate constant
b. Compute percent renal drug excretion
c. Determine elimination half-life
d. Determine elimination half-life if in the above situation renal excretion becomes totally impaired.
e. What is the impact of renal total impairment on elimination half-life of this drug?

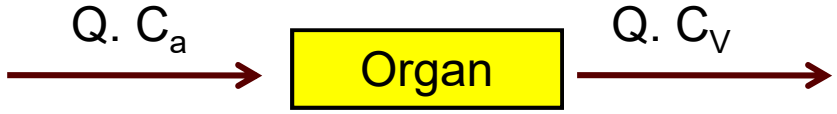
Clearance models : Compartmental & Physiologic models

1. Compartmental model:



$$Cl = Ke.Vd$$

2. Physiologic models:



- Clearance is the product of blood flow rate (Q) through an organ and the extraction ratio of that organ (E)

  Cl(organ) = Q(organ) x E(organ)

  where Organ extraction ratio (E) is given by:

$$E = \frac{[\text{Drug}]\text{in arterial blood} - [\text{Drug concentration in venous blood}}{\text{Drug concentration in arterial blood}} = \frac{Ca - Cv}{Ca}$$

Example-1

An antibiotic is given by IV bolus injection at a dose of 500 mg. The drug follows a one-compartment model. The total volume of distribution was 21 L and the elimination half-life was 6 hours. Urine was collected for 48 hours, and 400 mg of unchanged drug was recovered. Calculate k_E, $\mathbf{f_e}$, k_R, Cl_T, Cl_R, *and* Cl_{NR}.

Solution

$KE = 0.693/t_{1/2} = 0.693/6$ hrs $= 0.1155$/hr

$$\text{Fraction of drug excreted unchanged in urine, } fe = \frac{\text{Amount of drug excreted unchanged in urine}}{\text{Dose, if given IV then F} = 1} = \frac{400}{500} = 0.8$$

K_R = fe. KE = 0.8 x0.1155/hr = 0.0924 h^{-1}

$Cl_T = k_E \times V_{ss} = 0.1155 \times 21$ L = 2.43 L/h

$Cl_R = K_R$. Vd [steady state] = 0.0924 h^{-1} x 21 L = 1.94 L/hr

$Cl_{NR} = Cl_T - Cl_R = 2.43 - 1.94 = 0.49$ L/h

Example-2

If Viomycin plasma concentration after 300 mg I.V. Bolus administration is found to be 10.0 & 5.5 μg/ml at 2 & 4 hours respectively, assuming one-compartment kinetics, calculate:

a. Total systemic clearance in ml/min

b. Renal clearance in ml/min if fraction excreted unchanged in urine is 0.8

c. Non-renal clearance

c**Solution**

$CL_{total} = K_E.V_d = 0.004982*16500ml = 82.2$ ml/min

$CL_R = K_R * V_d = fe * kE * Vd$

$= 0.8 * 0.004982min^{-1} * 16500$ ml $= 65.76$ ml/min

$CL_{NR} = CL_{total} - CL_R$

$= 82.2 - 65.76 = 16.4376 = 16.44$ ml/min

11. Application of Pharmacokinetics to Clinical Situations

Clinical pharmacokinetics

- Discipline that applies **PK concepts & principles** in humans so as to design individualized dosage regimens to optimize therapeutic response of a medication while minimizing chance of adverse drug reaction

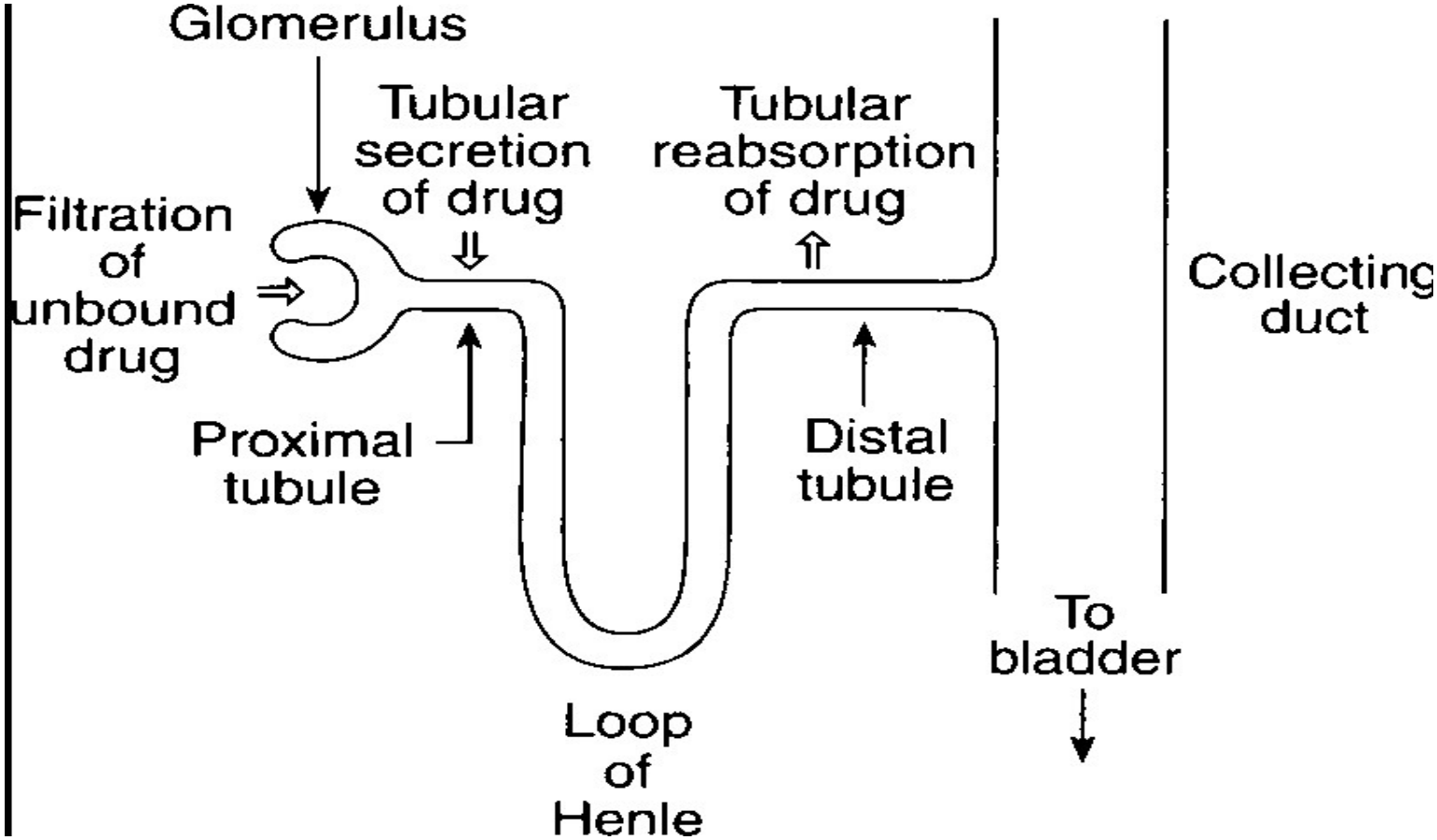
11.1. Pharmacokinetics in renal impairment

Introduction

- The kidney regulates body fluids, electrolyte balance, removes metabolic waste and excrete drug from the body
- Impairment or degeneration of kidney function due to disease, injury and/or drug intoxication affects pharmacokinetics of drugs.
  - Hypertension: may leads to renal insufficiency
  - Diabetes mellitus: may predispose patient to degenerative renal diseases
  - Hypovolemia: eventually lead to renal ischemia and damage due to reduction in renal blood flow
  - Nephrotoxic drugs/metals such as aminoglycosides, phenacetin, & heavy metals, such as mercury and lead may cause irreversible kidney damage

- Most water-soluble drugs are eliminated unchanged via kidney
- Water soluble drug metabolites that are formed via oxidation or conjugation are typically removed by renal excretion
- Unbound drug is filtered freely at the glomerulus as glomerular filtration is the primary elimination route for many medications that are small in size
- Drugs are actively secreted into urine, via proximal tubules by specific carriers or pumps that move drug from blood vessels in close proximity to the nephron into the proximal tubule

- Some drugs are reabsorbed from urine back into blood via tubular reabsorption at distal tubule
- Tubular reabsorption is influenced by pH of urine, pKa of drug & degree of drug molecular ionization
- Compounds that are not ionized in urine are more lipid soluble, better able to pass via lipid membranes & hence more prone to renal tubular reabsorption
- Therefore, nephron is responsible for removal of water soluble drug & /or metabolite from the body



Structure of Nephron along its tubular secretion and reabsorption sites

Effect of renal impairment on drug Absorption

- Absorption of drugs in patients with renal disorders could be inhibited by GI disturbances (nausea, vomiting, diarrhea) as seen in uremia, uremic gastritis, and pancreatitis
- Edema of GI tract can occur with nephritic syndrome and impair absorption
- Gastric motility can be impaired by uremia

Uraemia is a disorder caused by kidney failure

Outcome:

- ✓Retention of urea in the blood
- ✓Uremic person develops nausea, convulsions & in severe cases goes into a coma

- Gastric pH increases in chronic renal failure since urea is cleaved, yielding ammonia[Uremia] which buffers acid in the stomach
- Uremia increases gastric ammonia there by decreasing absorption of those drugs requiring acidic pH(eg: FeSO4)
- First-pass effect is reduced in patients with renal disease (thus, absorption is increased in drugs with high first pass effect, e.g. propranolol). **Why?**

  Reasons: Down regulation of CYP genes and competitive inhibition of protein binding
- Other drugs disclosing increased absorption : cloxacillin, propoxyphene, dihydrocodeine, zidovudine

Effect of Renal Failure on Protein Binding (PB) & VD

- ❖ Effect of a drug is related to amount of free or unbound drug available to target tissues
- ❖ Acidic drugs with high protein binding affinity (>80%) have decreased protein binding due to renal diseases

  Eg: **warfarin [99%], Phenytoin[90%]**

- Protein binding of basic drugs is usually normal or slightly decreased or increased (e.g.**quinidine, lidocaine)**
- **Hypoalbuinemia** is common to patients with renal failure. Hence drug with high plasma protein binding has less albumin to bind. What is the consequence?
- ❖ Uremic toxins may alter protein binding triggering increased conc. of free fraction of highly protein binding drug thereby altering actual VD effect. Eg Phenytoin.

What will happen to VD?

Drug elimination versus impaired kidneys

- Most drugs are eliminated through renal excretion or hepatic metabolism
- Kidney eliminates via filtration or active secretion
- Drugs with low Protien binding are filtered more readily
- As kidney disease progresses, kidney's ability to excrete uremic toxins & drugs decreases
- Patients with severe renal insufficiency can experience accumulation of metabolite(s) & unchanged drugs
- In patients with renal failure BBB is more permeable to such drugs as Cimetidine, Ranitidine & Famotidine due to uraemia facilitating access of drugs to CNS
- Metabolism of several drugs is reduced in renal failure

Summary: PK changes in AKI[Acute kidney injury]

1. Large volume of distribution due to:
   - increased extracellular fluid retention
   - increased plasma free drug level
2. Prolonged drug half-life due to:
   - ❖Reduced drug metabolism
   - ❖Reduced drug clearance
     - o declined GFR of drug
     - o decreased active tubular secretion of drug
     - o reduced hepatic clearance of drug
3. Increased free drug fraction due to:
   - ➢increased uremic toxin binding competition
   - ➢hypoalbuinemia

11.2. Pharmacokinetics in hepatic dysfunction

Introduction

- Hepatic disease can alter drug pharmacokinetics including absorption and disposition as well as pharmacodynamics including efficacy and safety
- Drugs are often metabolized by one or more enzymes located in cellular membranes of the liver
- Drugs and metabolites may also be excreted by biliary secretion but bile production decreases
- Hepatic disease may lead to drug accumulation, failure to form an active or inactive metabolite, increased bioavailability after oral administration and possible alteration in drug–protein binding

Impact of liver on drugs is vital for three reasons

1. Liver is the principal site for drug metabolism

- Liver disease may impair hepatic drug-metabolizing activity, the drugs themselves may also reduce these processes
- Hepatic drug metabolism can be decreased in AKI, since transcription and translation of CYP enzymes are reduced.
- This consideration applies primarily to **lipophilic drugs**, which are normally metabolized to hydrophilic compounds for urinary excretion

2. Impact of liver impairment on drug disposition

- Drug distribution is altered in liver disease.
- Reduced plasma albumin lowers plasma protein binding
- Accumulaton of bilirubin & other endogenous substances displace drugs from binding sites.
- In **ascites** ,V_D of hydrophilic drugs increases
- Reduced plasma binding of acidic drugs due to occurrence of low plasma protein levels
- Reduced biliary excretion (cholestasis) causes hyperbilirubinaemia and reduced excretion of drugs, e.g. *rifampicin and fusidic acid*

Note : Liver impairment affects metabolism, protein binding, V_D and drug elimination in the bile

***3.* Drugs may cause liver damage** e.g. *paracetamol*

11.3.Pharmacokinetic drug interactions

Definition

- Drug interaction is the modification of the effect [expected response] of one drug (object drug) in the patient by the prior concomitant administration of another drug (precipitant drug) in same patient

Object drug	Precipitant drug	Therapeutic effect
Phenytoin	Cimetidine	Phenytoin intoxication
Warfarin	Metronidazole	Bleeding
Warfarin	Barbiturate	Decreased anticoagulation
Oral contraceptive	Rifampicin	Pregnancy

Mechanisms of drug interactions

1. Pharmacodynamic drug interaction [PDDI]
2. Pharmacokinetics drug interaction [PKDI]
3. Pharmaceutical interaction

PKDI is a drug interaction in which ADMEs of the object drug are altered by precipitant, resulting in a changed plasma drug conc.

PKDI	Examples
Absorption	Drug interactions can affect rate & extent of systemic drug absorption (bioavailability) from the absorption site, resulting in increased or decreased drug BA
Distribution	Drug distribution may be altered by displacement of a drug from plasma protein or other binding sites due to competition for the same binding site
Hepatic Metabolism	Drugs that share the same drug-metabolizing enzymes have a potential for a drug interaction[Table-1]
Renal Excretion	Drugs that compete for active renal secretion may decrease renal clearance of the first drug. Probenecid blocks the active renal secretion of penicillin drugs [Table-2]

Table-1: **Hepatic Metabolism**

Interactions due to inhibition of CYP450 enzymes		
Phenytoin	Isoniazid, Cimetidine Chloramphenicol	Phenytoin intoxication
Warfarin	Allopurinol Metronidazole Phenylbutazone Co-trimoxazole	Haemorrhage
Theophylline	Cimetidine Erythromycin	Theophylline toxicity
Interactions due to induction of CYP450 enzymes		
Warfarin	Barbiturates Ethanol Rifampicin	Decreased anticoagulation
Oral contraceptives	Rifampicin	Pregnancy

Table-2 Drug interaction during excretion

Competitive interactions for renal tubular transport		
Primary [Object] drug	**Precipitant [Competing] drug**	**Effect of precipitant on object drug**
Penicillin	Probenecid	Increased penicillin blood level
Methotrexate	Salicylates Sulphonamides	Bone marrow suppression
Salicylate	Probenecid	Salicylate toxicity
Indometacin	Probenecid	Indometacin toxicity
Digoxin	Spironolactone Amiodarone Verapamil	Increased plasma digoxin

Pharmacodynamic drug interactions: Activity of object drug at its site of action is altered by the precipitant, directly or indirectly.

Direct PDDI: Drugs having similar or opposing pharmacologic effects are used concurrently, resulting in antagonistic, addition , potentiating or synergistic effects

Indirect PDDIs: Object & precipitant drugs have unrelated effects but the latter alters effects of the former, as in the case of slicylates that decrease ability of platelets to aggregate thereby impairing hemostasis if warfarin induced bleeding occurs

Note: The resultant effect of all PDDIs is altered drug action without a change in plasma drug conc.

PDDI	Examples
Synergism	Co-trimoxazole
Additive effect	Co-Amoxiclave
Potentiating effect	Penicillin & Probenecin
Antagonism	Amphetamine & alcohol

Pharmaceutical interactions are caused by a chemical or physical incompatibility when two or more drugs are mixed together in IV-infusion causing precipitation or inactivation of active principles as shown in the following table:

Mixture	Result
Thiopentone and suxamethonium	Precipitation
Diazepam and infusion fluids	Precipitation
Phenytoin &infusion fluids	Precipitation
Heparin and hydrocortisone	Inactivation of heparin
Gentamicin and hydrocortisone	Inactivation of gentamicin
Penicillin and hydrocortisone	Inactivation of penicillin
Ampicillin, Chlorpromazine or barbiturates in dextran solutions	Inactivation of the drugs

Outcomes of drug interactions

- Loss of therapeutic effect
- Toxicity
- Unexpected increase in pharmacological activity
- Beneficial (intended) effects e.g additive & potentiating or (unintended) antagonistic effects
- Chemical or physical interaction

Example

I.V incompatibility in fluid or syringes mixture

Prevention of drug interaction

1. Monitoring therapy and making adjustments
2. Monitoring blood level of some drugs with small therapeutic index e.g., digoxin, anticancer agents…etc
3. Monitoring some parameters that help to characterize early events of interaction or toxicity

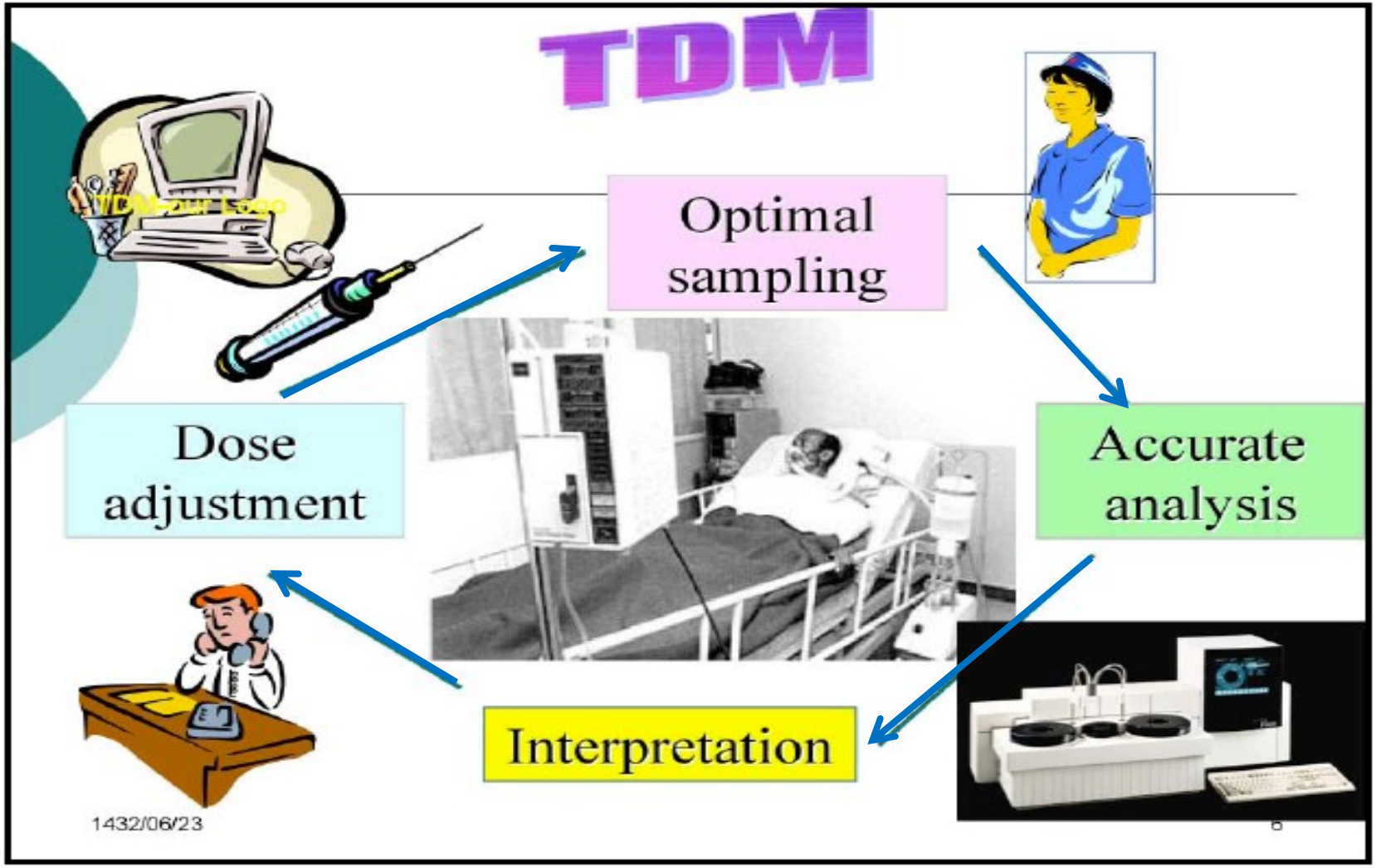
Example:

With warfarin administration, it is recommended to monitor prothrombin time to detect any change in the drug activity

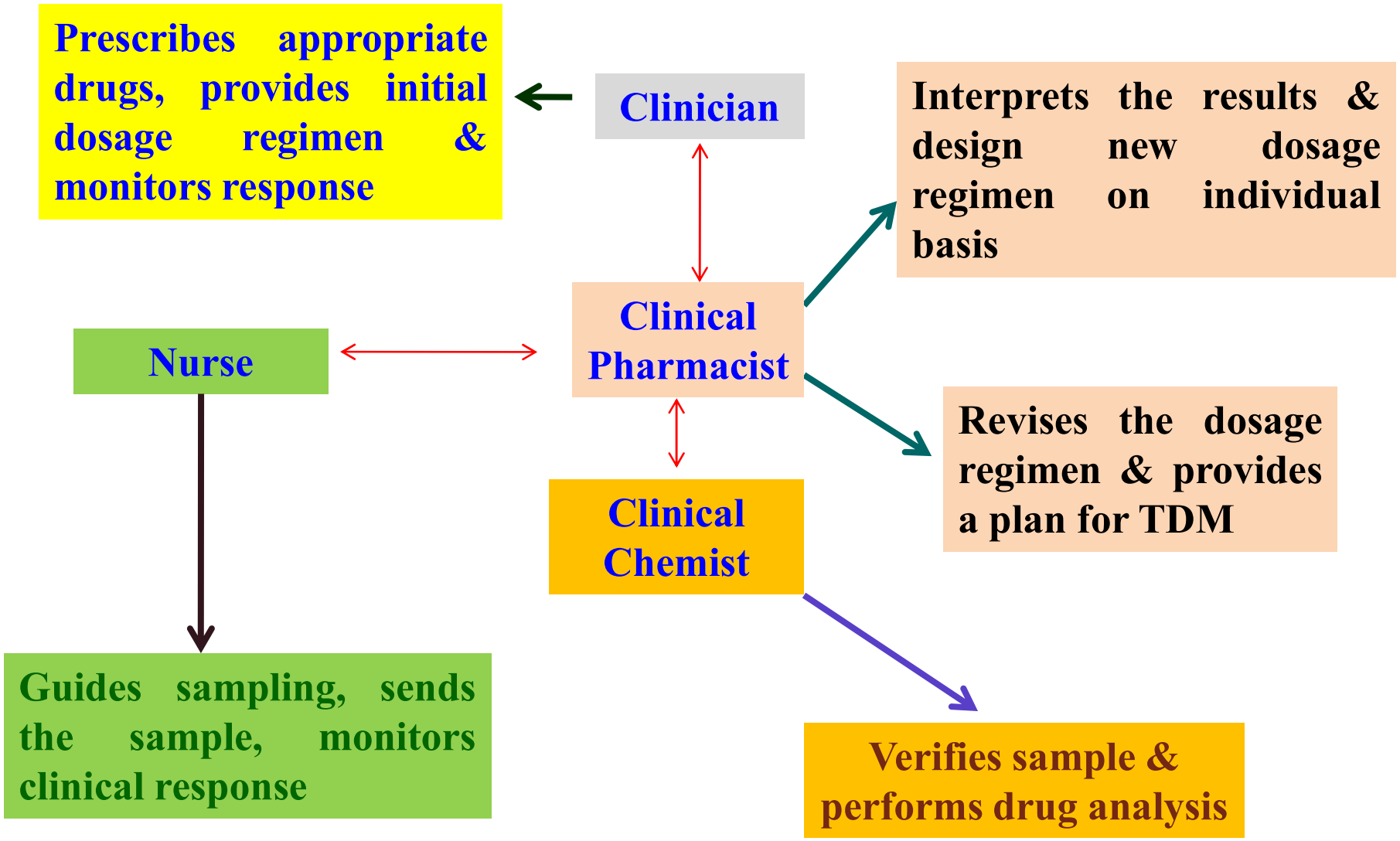
11.4.Therapeutic drug monitoring [TDM]

- It guides clinician to provide effective & safe drug therapy to individual patient
- It is a team work service where clinical pharmacist plays important role to guide the team. Why team?
- TDM involves not only measuring drug concentrations, but also clinical interpretation of result. These activities however require knowledge of pharmacokinetics, appropriate sample size & sampling time, drug history, patient's clinical condition & specific laboratory results

Note: Success of new drug therapy is highly dependent on reliable diagnosis, determination of delivery route, choice of drug, drug product & design of dosage regimen & consideration of patient's individualized pharmacokinetics and clinical condition or response



Schematic presentation of team based TDM


Prescribes appropriate drugs, provides initial dosage regimen & monitors response
Clinician
Interprets the results & design new dosage regimen on individual basis
Clinical Pharmacist
Nurse
Revises the dosage regimen & provides a plan for TDM
Clinical Chemist
Guides sampling, sends the sample, monitors clinical response
Verifies sample & performs drug analysis

Role of health professionals in a TDM service

Objective of Therapeutic Drug Monitoring

- Finding out an effective medication against the disease without any dangerous toxic action. How?
- By measuring blood medication levels, particularly those drugs with a narrow therapeutic range. Why?

Reasons:

- Insufficient plasma drug levels lead to under treatment or resistance
- Excessive levels lead to toxicity and tissue damage
- TDM when used properly helps to improve efficacy and minimize toxicity of selected drugs especially those with narrow therapeutic ranges or with marked pharmacokinetic variability

Therapeutic index (Therapeutic ratio)

- In **animal**,Therapeutic index is lethal dose of a drug for 50% of the population (LD_{50}) divided by minimum effective dose for 50% of population (ED_{50}).

$$\textbf{Therapeutic ratio} = \frac{\mathbf{LD_{50}}}{\mathbf{ED_{50}}}$$

- In **human** clinical trials; therapeutic index is the dose that produces toxicity in 50% of the population (TD_{50})divided by minimum effective dose for 50% of the population (ED_{50}).

$$\textbf{Therapeutic ratio} = \frac{\mathbf{TD_{50}}}{\mathbf{ED_{50}}}$$

Functions of a TDM service :

- Select drug
- Design dosage regimen
- Evaluate patient response
- Determine need for measuring serum drug conc.
- Assay for drug concentration in biological fluids
- Perform pharmacokinetic evaluation of drug conc.
- Readjust dosage regimen, if necessary
- Monitor serum drug concentrations
- Recommend special requirements

Indicators for Therapeutic Drug monitoring [TDM]

- Drug has narrow therapeutic range or small TI < 2
- Direct relationship exists between drug or drug metabolite levels in plasma and its pharmacological or toxic effects
- Therapeutic effect can not be readily assessed by clinical observation
- Existence of large individual variability in steady state plasma concentration
- Potential patient compliance problems
- Knowledge of the drug level influences management

Indicators ……cont

- **Poorly defined clinical end point**
- **Therapeutic failure**
- **Major organ failure**
- **Prevention of adverse drug effects**
- **Drugs with saturable metabolism**
- **Wide variation in the metabolism of drugs**
- **Availability of appropriate analytic techniques to determine drug & metabolite plasma levels**
  - Analytical method is said to be appropriate if it is sensitive, precise, accurate and specific enough to measure Serum Drug Concentration(SDC) within the reference range and allow rapid analysis to meet demand of emergency cases

TDM is unnecessary when:

- Clinical outcome is unrelated to dose or plasma conc.
- Dosage need not be individualized
- Pharmacological effects can be clinically quantified
- concentration effect relationship remains not established
- Drugs have wide therapeutic range such as beta blockers and calcium channel blockers.

Major causes of unexpected serum concentration in patients

- Genetic factors
- Non compliance
- Drug interactions
- Inappropriate dosage
- Altered protein binding
- Hepatic or renal disease
- Malabsorption of the drug
- Poor bioavailability of the drug

- Under these conditions, a dosage adjustment is made using the following formula for drugs with linear kinetics.

New dose/ Desired [drug] = Old dose/ Old [drug]

New dose =Old dose/Old [drug] x [Desired [drug]

Drugs subjected to TDM

Cardioactive drugs	**Amiodarone** **Digoxin,** **Digitoxin** **Quinidine** **Lignocaine** **Procainamide** **Propranolol**
Antibiotics	Gentamycin Kobramycin Amikacin
Antidepressants	Lithium Tricyclic-antidepressants

Antiepileptic	**Phenytoin** **Benzodiazepines** **Carbamazapine** **Phenobarbitone** **Ethosuximide** **Valproic acid**
Bronchodilator	Theophylline
Cancer chemo-therapy	Methotrexate
Immunosuppre-ssive	Cyclosporine

Therapeutic Range for Commonly Monitored Drugs	
Amikacin	20–30 μg/mL
Theophylline	10-20 *μg/mL*
Phenytoin	10-20 μg/mL
Quinidine	1–4 μg/mL
Valproic acid	50-100 μg/mL
Digoxin	1–2 ng/mL
Carbamazepine	4–12 μg/mL

Case history

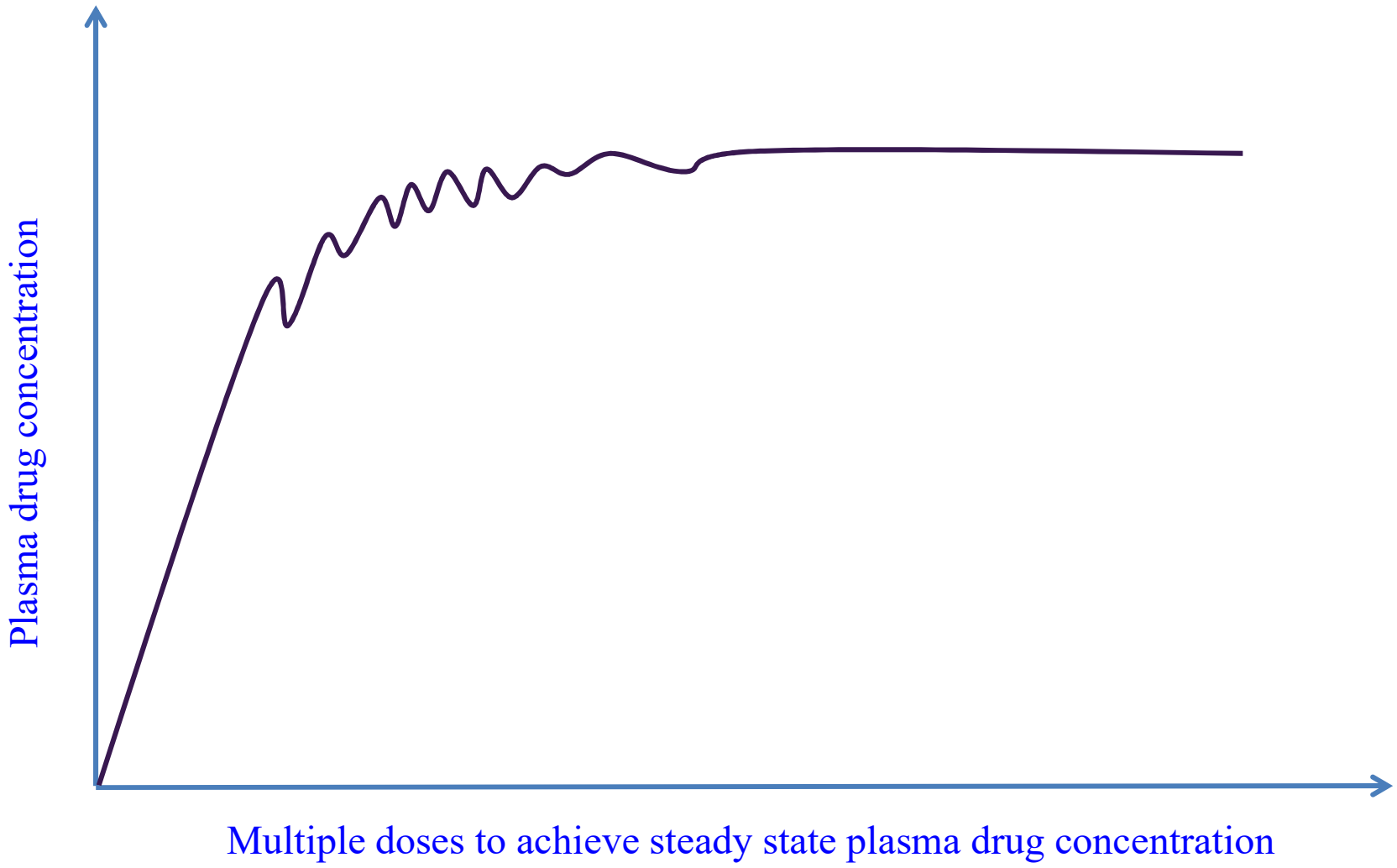
- A 35-year-old asthmatic is admitted to hospital at 6 a.m. because of a severe attack of asthma. She has been treated with salbutamol and beclometasone inhalers supplemented by a modified-release preparation of theophylline, 300mg at night. She has clinical evidence of a severe attack and does not improve with nebulized salbutamol and oxygen. Treatment with intravenous aminophylline is considered. Comment on precautions to be taken during or before conducting the procedure.

11.5. Multiple dosage regimen

- Some drugs, such as analgesics, neuromuscular blocking agents, hypnotics, bronchodilators, and antiemetics may be used effectively as a single dose
- More frequently, drugs are given on a continuous basis as a multiple doses
- Moreover, most drugs are administered with sufficient frequency that measurable and often pharmacologically significant levels of drug persist in the body when a subsequent dose is administered

- For drugs administered in a fixed dose at a constant dosing interval , the peak plasma level following the second and succeeding doses of a drug is almost always higher than the peak level after the first dose, and therefore the drug accumulates in the body relative to the initial dose. However, under these conditions drug accumulation proceeds at a decreasing rate with increasing number of doses until a steady-state plasma level of drug is achieved.
- At steady state, the plasma concentration of drug at any time during any dosing interval should be identical to the concentration at the same time during any other dosing interval.

n^{th} dose	% remaining assuming dosing interval = drug's half-life	% remaining	% Difference
1	100	100	0
2	50 + 100	150	50
3	25+ 50+ 100	175	25
4	12.5 +25+ 50+ 100	187.5	12.5
5	6.25 +12.5 +25+ 50+ 100	193.75	6.25
6	3.125 +6.25 +12.5 +25+ 50+ 100	196.875	3.125
7	1.5625 + 3.125 +6.25 +12.5 +25+ 50+ 100	197.438	1.5625
8	0.78125 +1.5625 + 3.125 +6.25 +12.5 +25+ 50+ 100	198.438	0.78125
9	0.390625 +0.78125 +1.5625 + 3.125 +6.25 +12.5 +25+ 50+ 100	198.828	0.390625
10	0.195+0.390625 +0.78125 +1.5625 + 3.125 +6.25 +12.5 +25+ 50+ 100	199.023	0.1953125
11	0.0975+0.195+0.390625 +0.78125 +1.5625 + 3.125 +6.25 +12.5 +25+ 50+ 100	199.121	0.09765625
12	0.04875+0.0975+0.195+0.390625 +0.78125 +1.5625 + 3.125 +6.25 +12.5 +25+ 50+ 100	199.145	0.0488281


Plasma drug concentration
Multiple doses to achieve steady state plasma drug concentration

Note:

- The rate and extent of accumulation of a drug is a function of the relative magnitudes of the dosing interval and the half-life of the drug
- The two main parameters to be adjusted in developing a dosage regimen:
    1. size of the drug dose
    2. frequency of drug administration (ie, the time interval between doses)

11.6. Clinical Pharmacokinetics of Aminoglycosides

They are highly polar cations ,hence very poorly absorbed from the gastrointestinal tract

- Less than 1% of a dose is absorbed after either oral or rectal administration
- The drugs are not inactivated in the intestine and are eliminated quantitatively in the faeces.
- Accumulation to toxic concentrations in patients with renal impairment may result from long-term oral or rectal uses or topical to large wounds, burns, or cutaneous ulcers
- All are absorbed rapidly from intramuscular injection site
- Have same peak plasma conc. after intramuscular injection & intravenous infusion of equal dose

Distribution

- Do not penetrate into most cells, CNS & eye due to **their polar nature**. Except for streptomycin, others have negligible binding to plasma albumin
- Their apparent VD is 25% of lean body weight

- Their concentrations in secretions & tissues are low.
- High concentrations are found only in renal cortex & endolymph & perilymph of the inner ear; causing nephrotoxicity & ototoxicity, respectively
- Administration of aminoglycosides to women late in pregnancy may result in accumulation of drug in fetal plasma and amniotic fluid.
- Streptomycin and tobramycin can cause hearing loss in children born to women who receive the drug during pregnancy

Dosing of aminoglycosides

- Give total daily dose as a single injection instead of two or three equally divided multiple doses. Why?

Reason: Once-daily total dosing regimen:

- ❖ is associated with less toxicity & equal effectiveness as multiple-dose regimens
- ❖ provides higher peak conc. & a longer period when concentrations fall below the threshold for toxicity than does a multiple-dose regimen
- ❖ enhnaces their concentration- dependent bactericidal activity and post-antibiotic effect

Exceptions : Accumulation likely to occur in pregnant, neonatal & pediatric infections, patient with creatinine clearances of less than 20 to 25 ml/min

Elimination

- All are excreted entirely by glomerular filtration
- A large fraction of administered dose is excreted unchanged during the first 24 hours, with most of this appearing in the first 12 hours.
- The half-lives of the aminoglycosides in plasma are similar and vary between 2 and 3 hours in patients with normal renal function

11.7. Clinical Pharmacokinetics of Digoxin

- Most digoxin tablets have on average 70% to 80% oral bioavailability
- If intramuscularly administered ,it causes erratic absorption, local discomfort & is not recommended
- The elimination half-life for Digoxin is 36 to 48 hours in patients with normal or near-normal renal function permitting once-a-day dosing
- Near steady-state blood levels are achieved one week after initiation of maintenance therapy
- Digoxin is excreted by the kidney with a clearance rate proportional to the glomerular filtration rate

11.8. Clinical Pharmacokinetics of Quinidine

- Well absorbed & 80% bound to plasma proteins [albumin]
- In high-stress states such as acute myocardial infarction greater than usual doses (and total plasma quinidine concentrations) may be required to maintain therapeutic concentrations of free quinidine
- Quinidine undergoes extensive hepatic oxidative metabolism, and approximately 20% is excreted unchanged by the kidneys
- Quinidine metabolism is induced by such drugs as phenobarbital and phenytoin calling for very high doses of quinidine to achieve therapeutic concentrations in patients receiving these agents.

11.9. Clinical Pharmacokinetics of Phenytoin

- It is available as rapid-release and extended-release oral formulations
- Once-daily dosing is possible only with the extended release formulations
- PK characteristics of phenytoin are influenced by its binding to serum proteins, nonlinearity of its elimination kinetics &metabolism by CYPs
- 90% bound to serum proteins, mainly albumin.
- Elimination of phenytoin varies as a function of its concentration [nonlinear elimination rate]

- Plasma half-life of phenytoin increases with increased plasma conc. above10 µg/ml ; below 10 µg/ml it is 6 to 24 hours .As a result, plasma drug concentration increases disproportionately as dosage is increased, even with small adjustments for levels near the therapeutic range
- 95% of phenytoin undergo hepatic metabolism
- Phenytoin inhibits or induces hepatic enzyme

Example

- Phenytoin + warfarin may cause bleeding disorder
- Phenytoin + oral contraceptive may lead to unplanned pregnancy

11.10. Pharmacokinetic of phenobarbital

- Oral absorption of phenobarbital is complete but slow
- Peak plasma concentrations occur several hours after a single dose
- 40% to 60% bound to plasma proteins & in tissues, including brain
- Up to 25% of a dose is eliminated by pH-dependent renal excretion of unchanged drug; the remainder is inactivated by hepatic metabolism
- Phenobarbital + oral contraceptives leads to unplanned pregnancy as the later is metabolized by induced CYP_3A_4

11.11. Pharmacokinetic of valproate [Valproic acid]

- Absorbed rapidly & completely after oral administration
- Peak plasma concentration is observed in 1 to 4 hours [delayed for enteric-coated tablets or ingested with meals]
- The apparent VD for valproate is about 0.2 L/kg
- 90% plasma proteins bound
- 95% of valproate undergoes hepatic metabolism, with less than 5% excreted unchanged in urine

11.12. Immuno-suppressants : cyclosporine & tacrolimus

A. Cyclosporine: Used during organ transplantation due to its immunosuppressive activity

- After oral administration its absorption is incomplete & varies with individual patient & formulation used
- Food affects its absorption
- Distributed extensively outside the vascular compartment
- Extensively metabolized in the liver by CYP3A and to a lesser degree by the gastrointestinal tract and kidneys
- Only 0.1% is excreted unchanged in urine
- Dose individualization is needed since its clearance shows inter patient variability
- In hepatic dysfunction, dosage adjustments are required but not in case of renal failure

B. Tacrolimus

- Food decreases rate & extent of its absorption.
- Plasma protein binding is from 75% to 99%
- Its half-life is about 12 hours
- Extensively metabolized in the liver
- Largely excreted in faeces and only less than1% of administered dose is excreted unchanged in the urine
- Because of inter-subject variability in pKs, individualized dosing is required for optimal therapy
- Dose adjustment is also indicated in hepatic dysfunctioning